STIC Search Report
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STIC Database Tracking Number: 196064

TO: Roy Issac **Location: REM-5D24&5C18** **Art Unit: 1623** **July 21, 2006** **Case Serial Number: 10/736301**	**From: P. Sheppard** **Location: Remsen Building** **Phone: (571) 272-2529** **sheppard@uspto.gov**

Search Notes

ACCESS DB # 196064

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Roy Issac Examiner # : 82353 Date: 7/21/06
Art Unit: 1623 Phone Number: 2-2671 Serial Number: 10736301
Location (Bldg/Room#): 5D24 (Mailbox #): 5C18 Results Format Preferred (circle): PAPER DISK
****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: BIB Datasheet attached

Inventors (please provide full names):

Earliest Priority Date:

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

Please search structure I in claim 1 & its use in HIV

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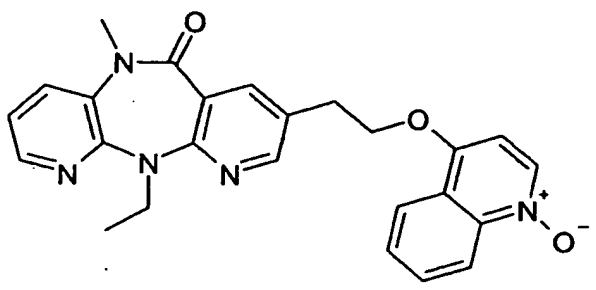
1. A method for treating HIV-1 infection in a human suffering from HIV-1 infection, which method comprises co-administering a compound of the formula I



I

or a pharmaceutically acceptable salt thereof and one or more inhibitors of CYP 450, the latter being administered in an amount which is sufficient to reduce the metabolism of the compound of the formula I by CYP 450 by at least half.

2. The method of claim 1 wherein the amount of the compound of the formula I

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     (FILE 'REGISTRY' ENTERED AT 17:30:01 ON 21 JUL 2006)
                DEL HIS Y
L1              STR
L3           31 SEA SSS FUL L1

     FILE 'HCAPLUS' ENTERED AT 18:00:59 ON 21 JUL 2006
L4            4 SEA ABB=ON  PLU=ON  L3
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                OR "CORDINGLEY MIKE"/AU OR "CORDINGLEY MIKE G"/AU)
L6           60 SEA ABB=ON  PLU=ON  L5 NOT L4
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     FILE 'REGISTRY' ENTERED AT 18:02:46 ON 21 JUL 2006
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     FILE HCAPLUS

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     FILE LAST UPDATED: 20 Jul 2006  (20060720/ED)

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     STRUCTURE FILE UPDATES:   20 JUL 2006  HIGHEST RN 894992-91-7
     DICTIONARY FILE UPDATES:  20 JUL 2006  HIGHEST RN 894992-91-7

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

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FILE COVERS 1907 - 21 Jul 2006 VOL 145 ISS 5
FILE LAST UPDATED: 20 Jul 2006 (20060720/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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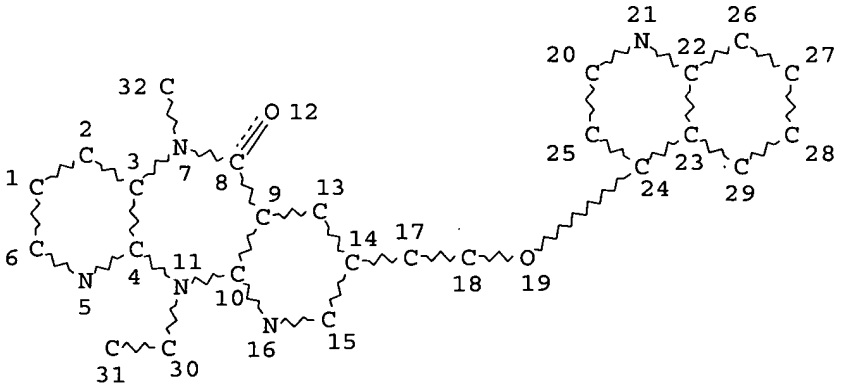
L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE
L3 31 SEA FILE=REGISTRY SSS FUL L1
L4 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L3

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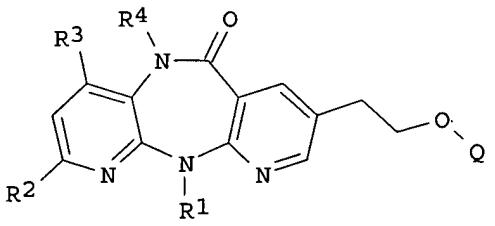
=> d ibib abs hitstr l4 1-4

L4 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:445778 HCAPLUS
DOCUMENT NUMBER: 144:468213
TITLE: Process for preparation of diazepine N-oxide derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors
INVENTOR(S): Meyer, Oliver; Heddesheimer, Ingo; Zerban, Georg
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Gmbh & Co. KG, Germany
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006048425	A1	20060511	WO 2005-EP55706	20051102
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006100200	A1	20060511	US 2005-264281	20051101
PRIORITY APPLN. INFO.:			EP 2004-26241 A	20041105

OTHER SOURCE(S): MARPAT 144:468213
GI



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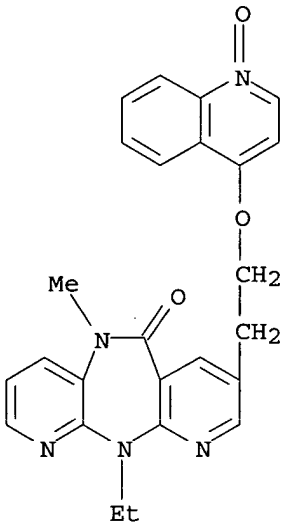
AB The invention provides a process for preparing N-oxides of diazepine derivs. I [wherein R1 = Me, Et, cyclopropyl, Pr, iso-Pr, or cyclobutyl; R2 = H, F, Cl, alkyl, cycloalkyl, or CF3; R3 = H or Me, R4 = H, Me, or Et; Q = 1-oxido-4-quinolinyl or 1-oxido-5-quinolinyl] or pharmaceutically acceptable salts thereof, comprising oxidation of the corresponding diazepine derivs. under phase-transfer conditions. For example, I (R1 = Et; R2 and R3 = H; R4 = Me; Q = 4-quinolinyl) was treated with OXONE in CH2Cl2/water

in the presence of tetrabutylammonium hydrogensulfate and acetone to give I (R1 = Et; R2 and R3 = H; R4 = Me; Q = 1-oxido-4-quinolinyl) with 99.3% purity. The title compds. are effective inhibitors of HIV reverse transcriptase (no data).

IT 380378-81-4P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of N-oxides of diazepine derivs. as non-nucleoside HIV-1 reverse transcriptase inhibitors)

RN 380378-81-4 HCAPLUS

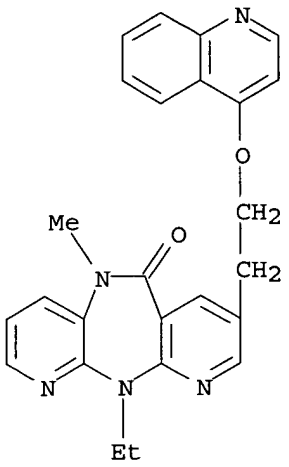
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



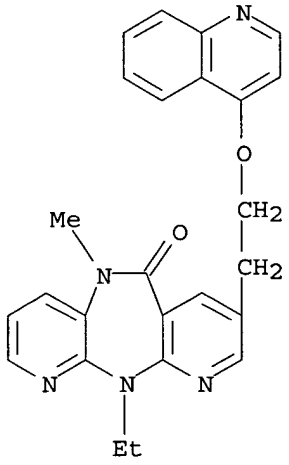
IT 380378-84-7 886468-35-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-oxides of diazepine derivs. as non-nucleoside HIV-1 reverse transcriptase inhibitors)

RN 380378-84-7 HCAPLUS

CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



RN 886468-35-5 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1078236 HCAPLUS
DOCUMENT NUMBER: 143:353310
TITLE: Crystalline forms of 5, 11-dihydro-11-ethyl-5-methyl-8-{2-{(1-oxido-4-quinolinyl)oxy}ethyl}-6H-dipyrido[3,2-b:2',3'-e] [1,4]diazepin-6-one and methods for preparation
INVENTOR(S): Busacca, Carl A.; Cerreta, Michael; Varsolona,

Richard; Smoliga, John; Lorenz, Jon; Vitous, Jana
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany
SOURCE: U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005222134	A1	20051006	US 2005-83401	20050318
WO 2005097796	A2	20051020	WO 2005-US9655	20050323
WO 2005097796	A3	20060105		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

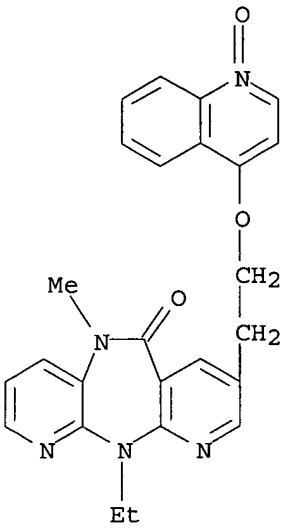
PRIORITY APPLN. INFO.: US 2004-559354P P 20040402

AB The present invention comprises the discovery of a dihydrate crystalline form of 5,11-dihydro-11-ethyl-5-methyl-8-{2-{(1-oxido-4-quinolinyl)oxy}ethyl} -6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, which is thermodynamically or kinetically favored at temps. and humidity's that are most likely to be encountered upon storage of drug substance or drug product and thus pharmaceutically preferred to the trihydrate that is provided by the prior art. The invention also comprises methods for making this dihydrate crystalline form. The invention further discovers that under proper conditions several anhydrous polymorphs of 5,11-dihydro-11-ethyl-5-methyl-8-{2-{(1-oxido-4-quinolinyl)oxy} ethyl}-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one may be formed. One of these, which is designated as anhydrous Form III (AF III), has demonstrated phase stability at some tested ambient conditions, which indicates that it is pharmaceutically acceptable, and biol. testing has shown that it leads to higher plasma levels than are attainable using other crystalline forms of the drug. Thus, the invention further includes anhydrous Form III of 5,11-dihydro-11-ethyl-5-methyl-8-{2-{(1-oxido-4-quinolinyl)oxy}ethyl} -6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one and methods for its manufacture

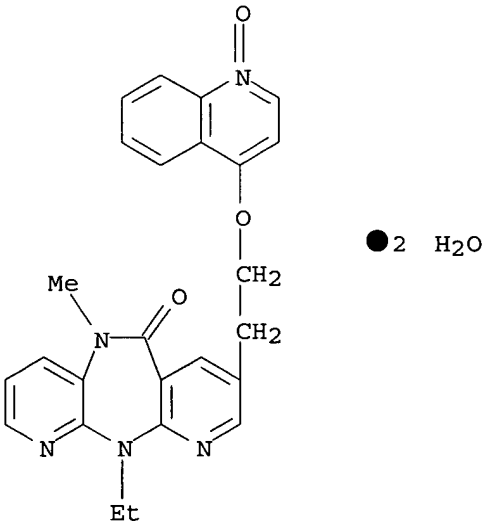
IT 380378-81-4 865887-44-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystalline forms of 5, 11-dihydro-11-ethyl-5-methyl-8-{2-{(1-oxido-4-quinolinyl)oxy}ethyl}-6H-dipyrido[3,2-b:2',3'-e] [1,4]diazepin-6-one and methods for preparation)

RN 380378-81-4 HCAPLUS

CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



RN 865887-44-1 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, dihydrate (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:531365 HCAPLUS
DOCUMENT NUMBER: 141:65063
TITLE: Use of a combination containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) with an inhibitor of cytochrome p450 for the treatment of HIV-1 infection
INVENTOR(S): Cordingley, Michael Graham
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

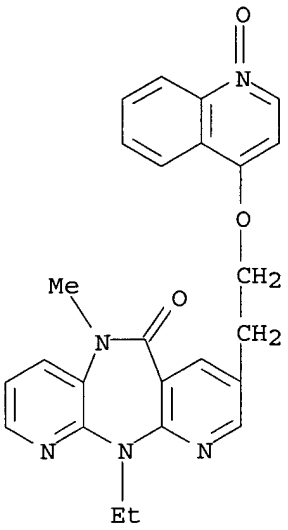
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004054586	A1	20040701	WO 2003-EP14224	20031215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2510143	AA	20040701	CA 2003-2510143	20031215
AU 2003296647	A1	20040709	AU 2003-296647	20031215
US 2004152625	A1	20040805	US 2003-736301	20031215
EP 1575595	A1	20050921	EP 2003-813119	20031215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017095	A	20051025	BR 2003-17095	20031215
CN 1726041	A	20060125	CN 2003-80106301	20031215
JP 2006511538	T2	20060406	JP 2004-560402	20031215
NO 2005003455	A	20050810	NO 2005-3455	20050715
PRIORITY APPLN. INFO.:			US 2002-433690P P	20021216
			WO 2003-EP14224 W	20031215

AB An improved method for using a NNRTI in the treatment of HIV-1 infection comprises administering to a human in need of treatment for HIV-1 infection a therapeutically effective amount of the NNRTI, or a pharmaceutically acceptable salt thereof, and an amount of an inhibitor of cytochrome P 450 that is sufficient to elevate, enhance, or extend plasma concns. of said NNRTI.

IT 380378-81-4
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-nucleoside reverse transcriptase inhibitor combination with cytochrome P 450 inhibitor for treatment of HIV-1 infection)

RN 380378-81-4 HCAPLUS

CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



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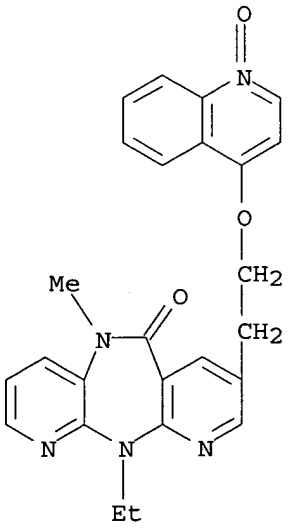
710282-35-2 710282-36-3 710282-37-4
710282-38-5 710282-39-6 710282-40-9
710282-41-0 710282-42-1 710282-43-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-nucleoside reverse transcriptase inhibitor combination with cytochrome P 450 inhibitor for treatment of HIV-1 infection)

RN 380378-81-4 HCAPLUS

CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



RN 710282-28-3 HCAPLUS

CN Carbamic acid, [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-

2-hydroxy-1-(phenylmethyl)propyl]-, (3S)-tetrahydro-3-furanyl ester, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

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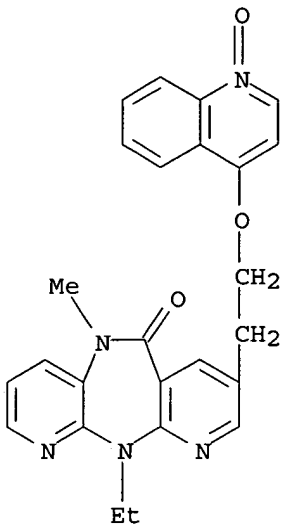
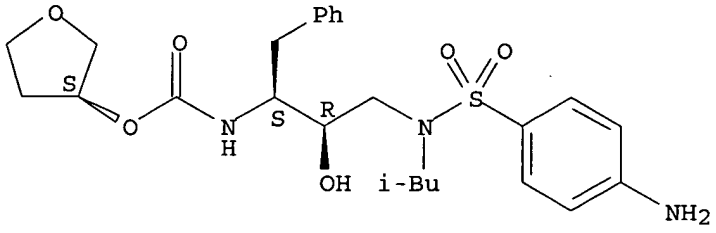
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 161814-49-9
CMF C25 H35 N3 O6 S

Absolute stereochemistry.



RN 710282-29-4 HCAPLUS
CN 2,5,6,10,13-Pentaazatetradecanedioic acid, 3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-, dimethyl ester, (3S,8S,9S,12S)-, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

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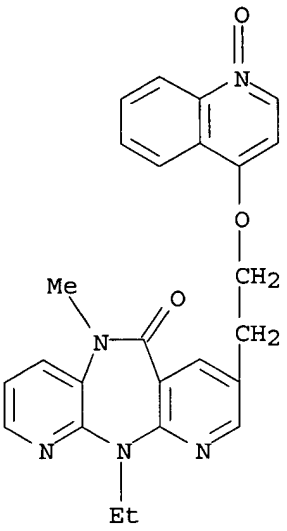
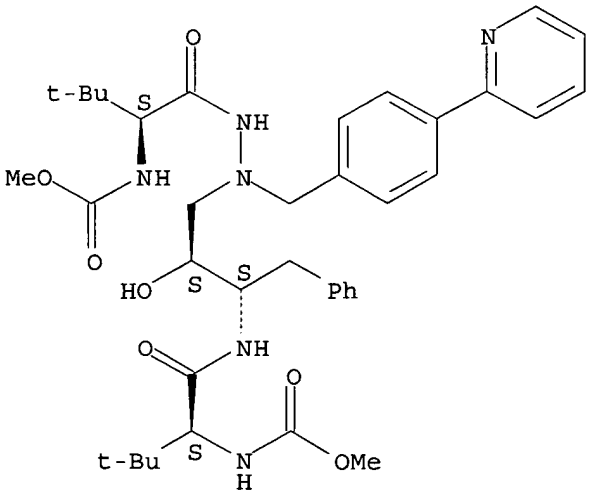


CM 2

CRN 198904-31-3
CMF C38 H52 N6 O7

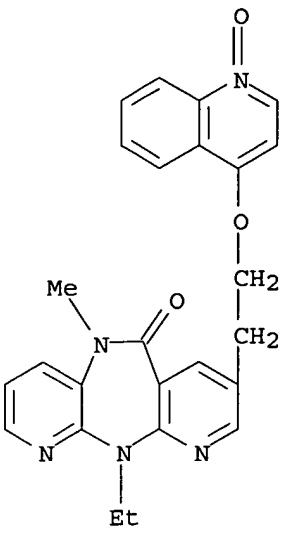
Absolute stereochemistry. Rotation (-).



RN 710282-30-7 HCAPLUS
CN Erythromycin, 6-O-methyl-, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

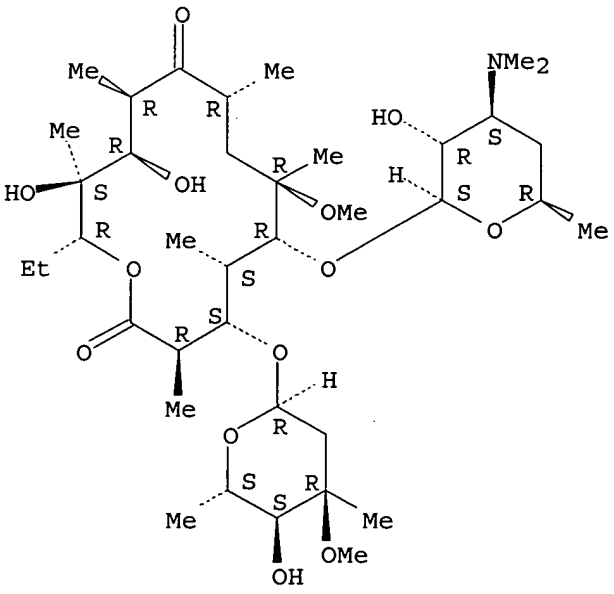
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 81103-11-9
CMF C38 H69 N O13

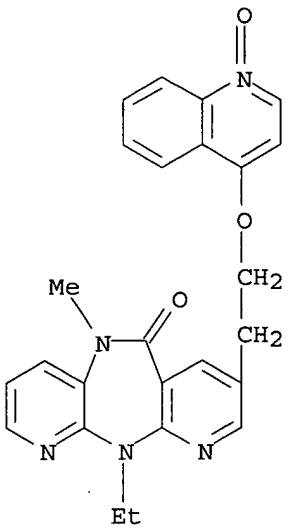
Absolute stereochemistry.



RN 710282-31-8 HCAPLUS
CN Cyclosporin, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

CRN 380378-81-4
CMF C25 H23 N5 O3



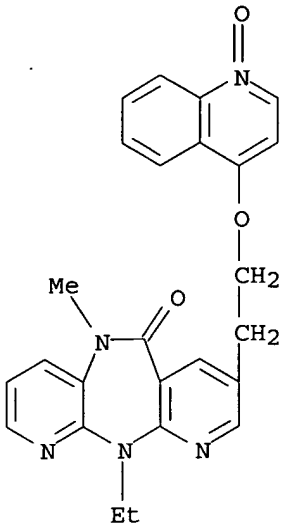
CM 2

CRN .79217-60-0
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 710282-32-9 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with (2S,3S)-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (9CI) (CA INDEX NAME)

CM 1

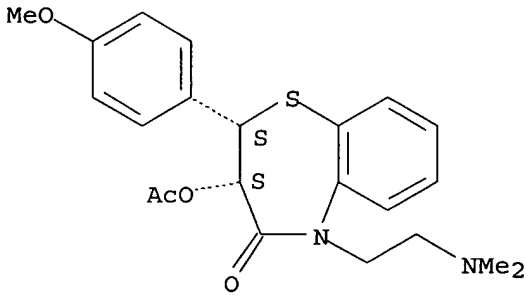
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 42399-41-7
CMF C22 H26 N2 O4 S

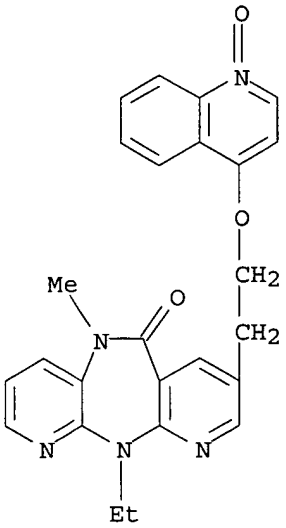
Absolute stereochemistry. Rotation (+).



RN 710282-33-0 HCAPLUS
CN Erythromycin, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

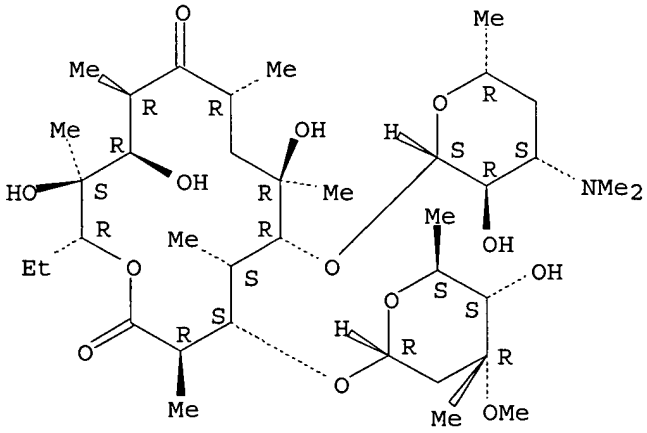
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 114-07-8
CMF C37 H67 N O13

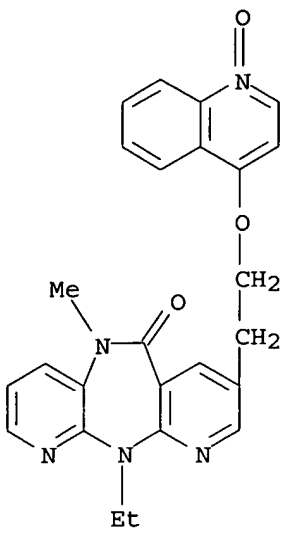
Absolute stereochemistry. Rotation (-).



RN 710282-34-1 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one (9CI) (CA INDEX NAME)

CM 1

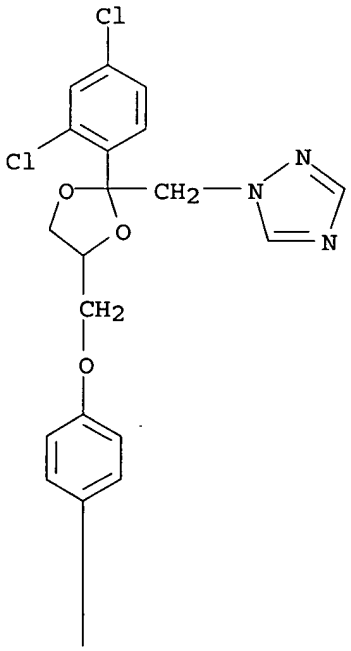
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 84625-61-6
CMF C35 H38 Cl2 N8 O4

PAGE 1-A



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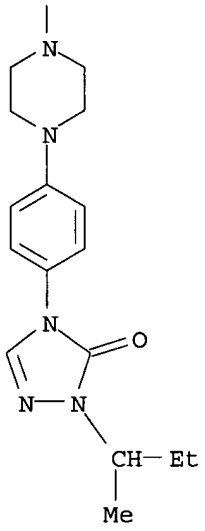
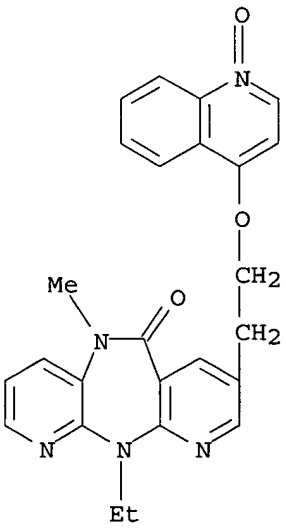


RN 710282-35-2 HCAPLUS
CN D-erythro-Pentonamide, 2,3,5-trideoxy-N-[(1S,2R)-2,3-dihydro-2-hydroxy-1H-inden-1-yl]-5-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

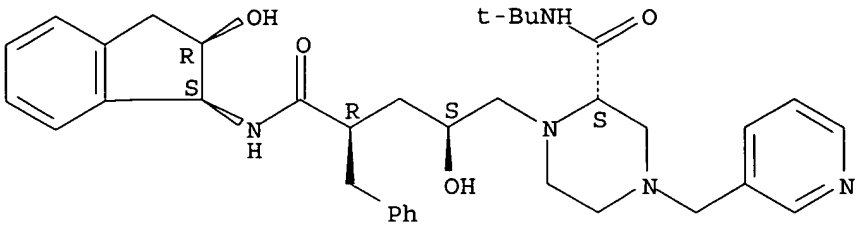
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 150378-17-9
CMF C36 H47 N5 O4

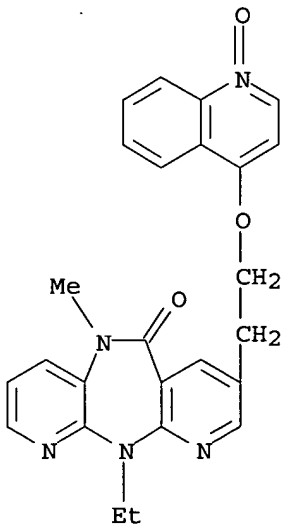
Absolute stereochemistry.



RN 710282-36-3 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with rel-1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (9CI) (CA INDEX NAME)

CM 1

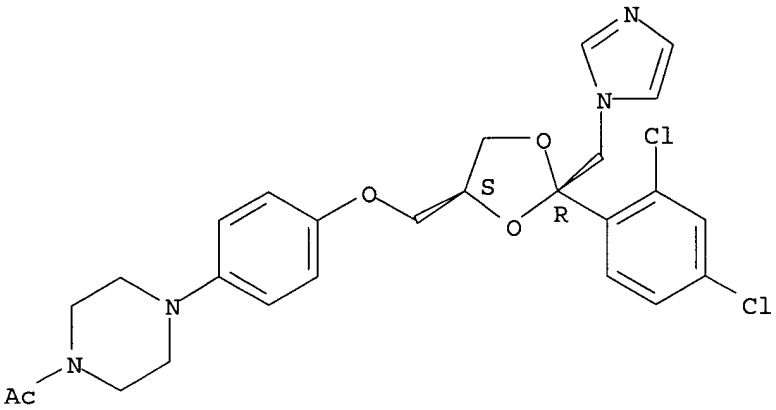
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 65277-42-1
CMF C26 H28 Cl2 N4 O4

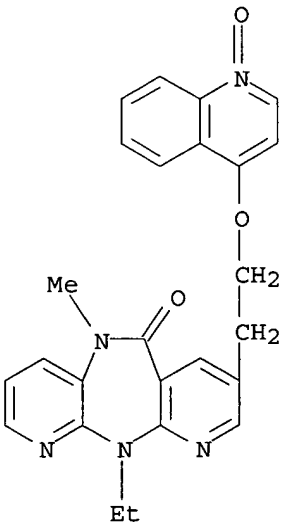
Relative stereochemistry.



RN 710282-37-4 HCAPLUS
CN Acetic acid, methoxy-, (1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl ester, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

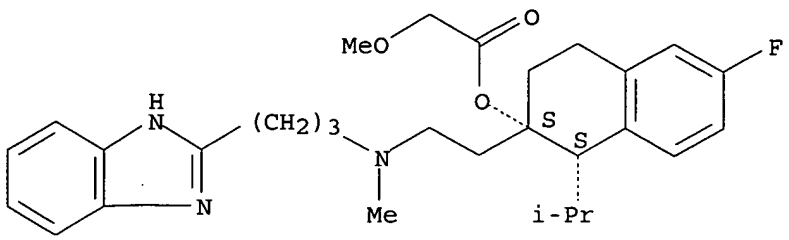
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 116644-53-2
CMF C29 H38 F N3 O3

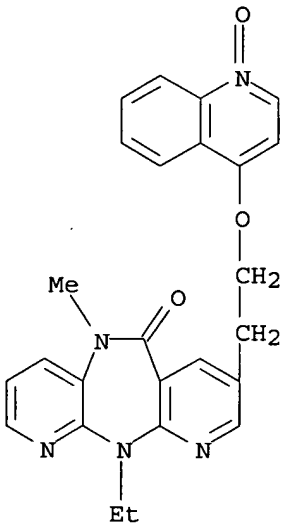
Absolute stereochemistry.



RN 710282-38-5 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one (9CI) (CA INDEX NAME)

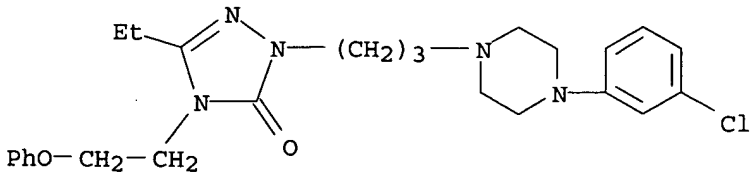
CM 1

CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 83366-66-9
CMF C25 H32 Cl N5 O2

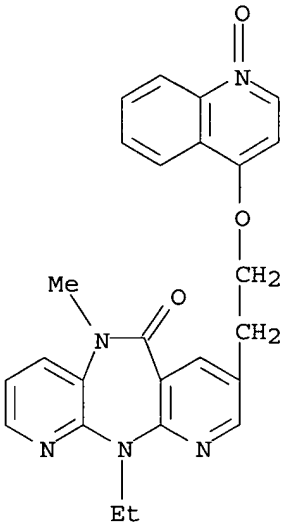


RN 710282-39-6 HCAPLUS
CN 3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-[(2R,3R)-2-

hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-, (3S,4aS,8aS)-, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

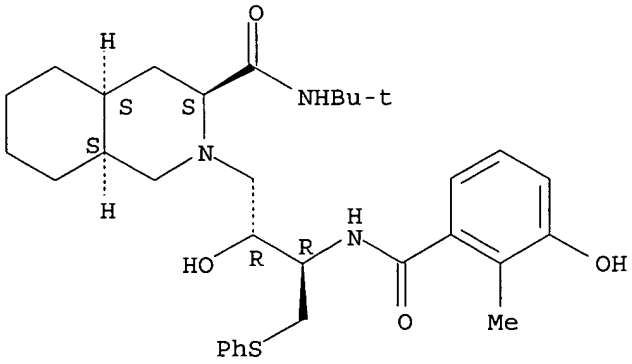
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 159989-64-7
CMF C32 H45 N3 O4 S

Absolute stereochemistry.

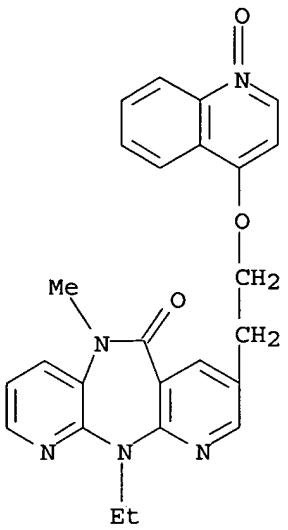


RN 710282-40-9 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-,mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-

dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

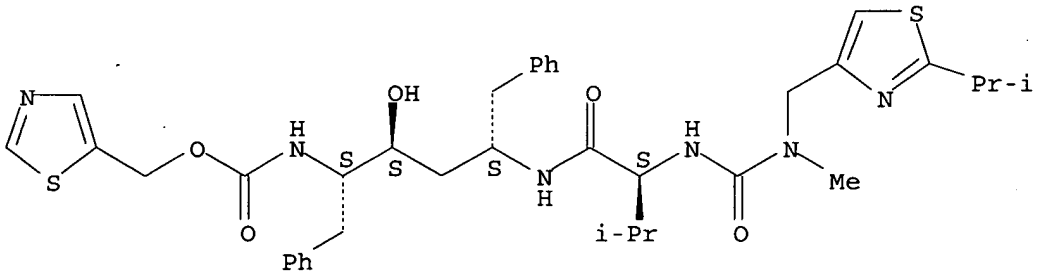
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

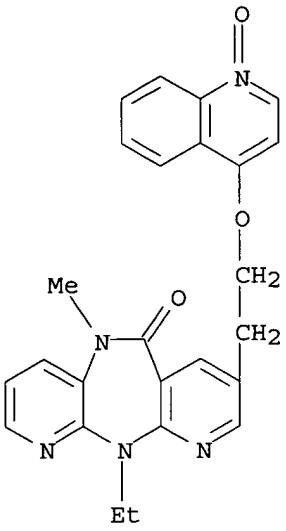
Absolute stereochemistry.



RN 710282-41-0 HCAPLUS
CN Vitamin E, mixt. with 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one (9CI) (CA INDEX NAME)

CM 1

CRN 380378-81-4
CMF C25 H23 N5 O3



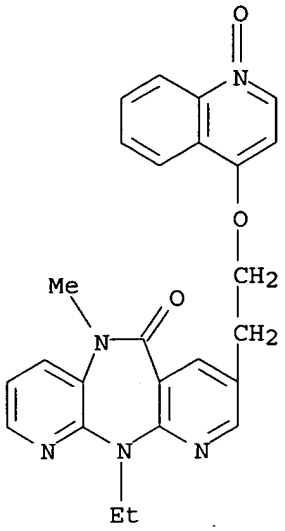
CM 2

CRN 1406-18-4
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 710282-42-1 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with 4-[[(2E)-3,7-dimethyl-2,6-octadienyl]oxy]-7H-furo[3,2-g][1]benzopyran-7-one (9CI) (CA INDEX NAME)

CM 1

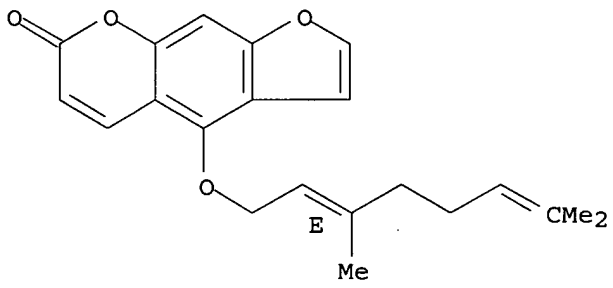
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 7380-40-7
CMF C21 H22 O4

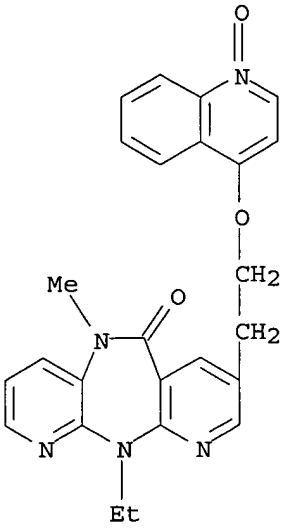
Double bond geometry as shown.



RN 710282-43-2 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-, mixt. with 4-[[(2E)-6,7-dihydroxy-3,7-dimethyl-2-octenyl]oxy]-7H-furo[3,2-g][1]benzopyran-7-one (9CI) (CA INDEX NAME)

CM 1

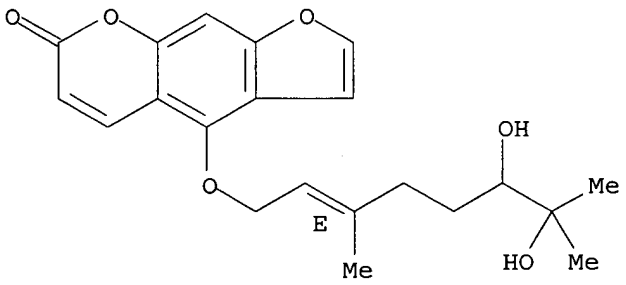
CRN 380378-81-4
CMF C25 H23 N5 O3



CM 2

CRN 145414-76-2
CMF C21 H24 O6

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:923799 HCAPLUS
DOCUMENT NUMBER: 136:37632
TITLE: Preparation of non-nucleoside reverse transcriptase inhibitors
INVENTOR(S): Simoneau, Bruno
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

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			WO 2001-CA890 W	20010614

OTHER SOURCE(S): MARPAT 136:37632

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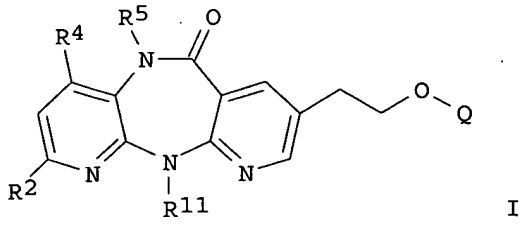

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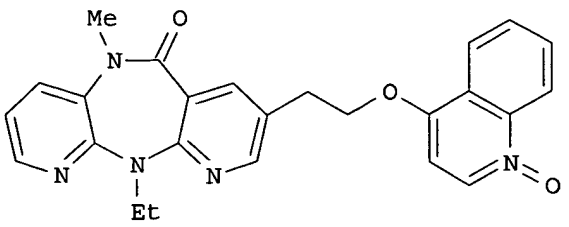


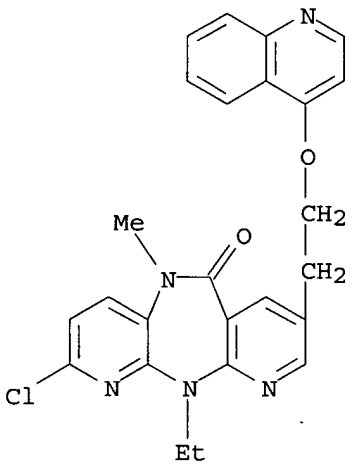
II

AB Compds. of formula I [R2 = H, F, Cl, (C1-4) alkyl, (C3-4) cycloalkyl, CF3;

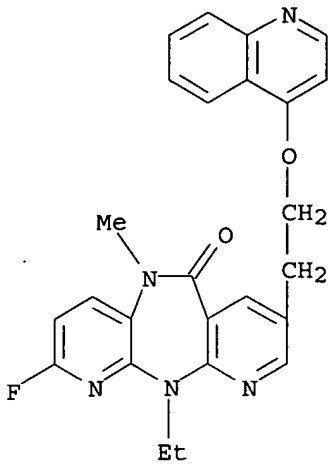
R4 = H, Me; R5 = H, Me, Et; R4 and R5 are not both Me, and if R4 is Me then R5 cannot be Et; R11 = Et, cyclopropyl, Pr, iso-Pr, isobutyl; Q = 4- or 5-quinolinyl or their 1-oxides] are prepared as inhibitors of HIV reverse transcriptase, wild-type and several mutant strains. Thus, II was prepared in several steps from 2-chloro-3-nitropyridine, ethylamine, 5-bromo-2-chloro-3-pyridinecarbonyl chloride and 4-hydroxyquinoline. II was shown to inhibit wild-type and mutant strains of reverse transcriptase in assays.

IT 380378-63-2P 380378-65-4P 380378-73-4P
380378-77-8P 380378-81-4P 380378-84-7P
380378-86-9P 380378-87-0P 380378-88-1P
380378-97-2P 380379-39-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dipyridodiazepinone derivs. as reverse transcriptase inhibitors)

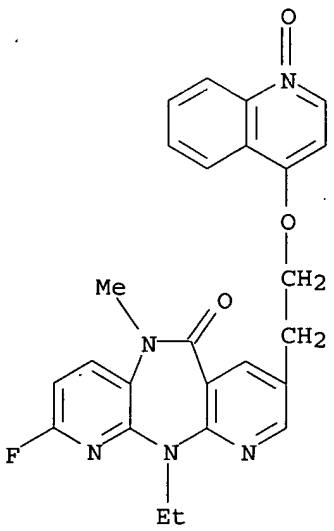
RN 380378-63-2 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 2-chloro-11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



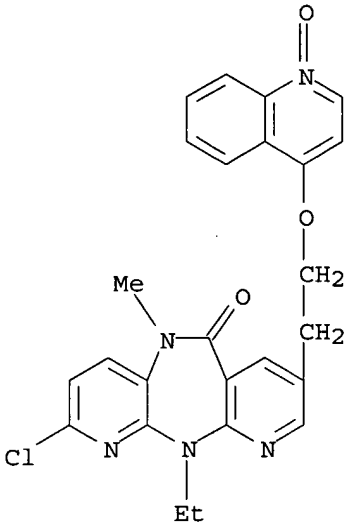
RN 380378-65-4 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-2-fluoro-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



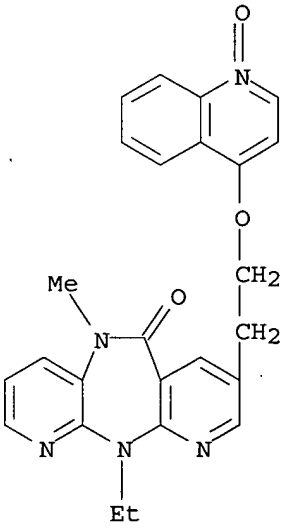
RN 380378-73-4 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-2-fluoro-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



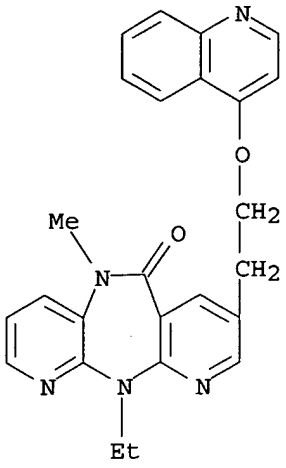
RN 380378-77-8 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 2-chloro-11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



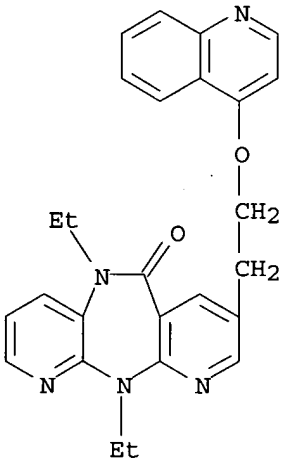
RN 380378-81-4 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



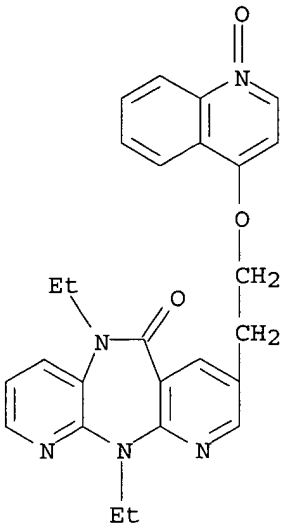
RN 380378-84-7 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



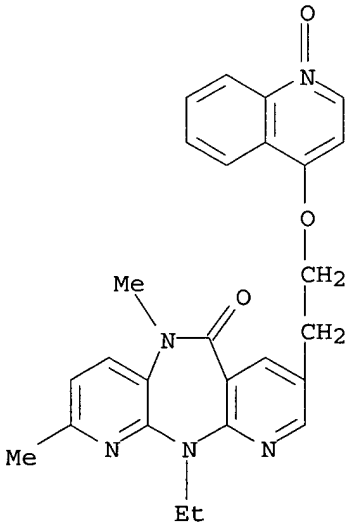
RN 380378-86-9 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 5,11-diethyl-5,11-dihydro-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



RN 380378-87-0 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 5,11-diethyl-5,11-dihydro-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



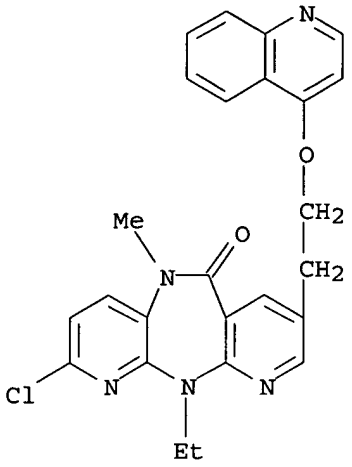
RN 380378-88-1 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-2,5-dimethyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]- (9CI) (CA INDEX NAME)



RN 380378-97-2 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 2-chloro-11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

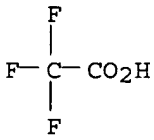
CM 1

CRN 380378-63-2
CMF C25 H22 Cl N5 O2

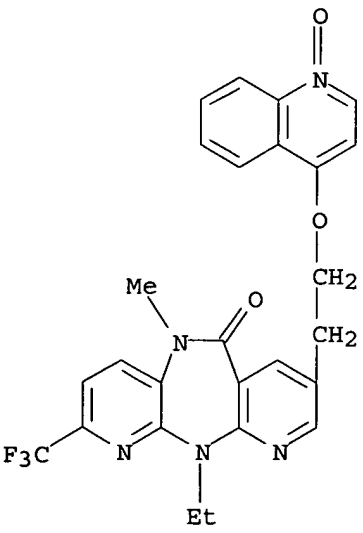


CM 2

CRN 76-05-1
CMF C2 H F3 O2

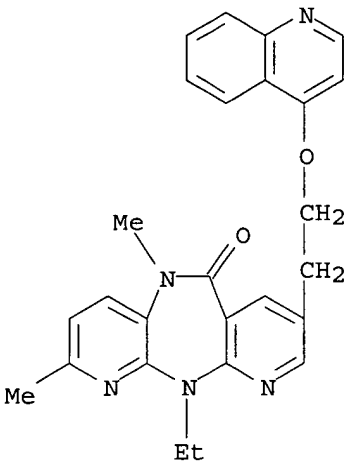


RN 380379-39-5 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)

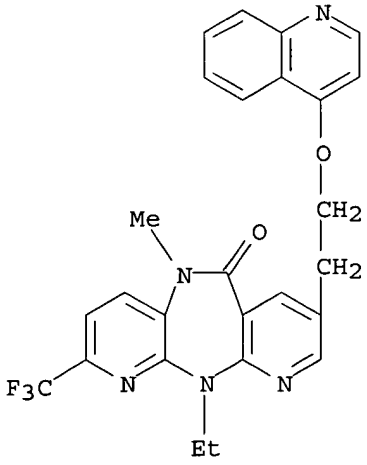


IT 380379-29-3P 380379-37-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dipyridodiazepinone derivs. as reverse transcriptase inhibitors)

RN 380379-29-3 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-2,5-dimethyl-8-[2-(4-quinolinyloxy)ethyl]- (9CI) (CA INDEX NAME)



RN 380379-37-3 HCAPLUS
CN 6H-Dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, 11-ethyl-5,11-dihydro-5-methyl-8-[2-(4-quinolinyloxy)ethyl]-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3           31 SEA FILE=REGISTRY SSS FUL L1
L4            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L5           61 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("CORDINGLEY M"/AU OR
                "CORDINGLEY M G"/AU OR "CORDINGLEY MICHAEL G"/AU OR "CORDINGLEY
                 MICHAEL GRAHAM"/AU OR "CORDINGLEY MIKE"/AU OR "CORDINGLEY
                MIKE G"/AU)
L6           60 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 NOT L4


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=> d ibib abs l6 1-60

L6   ANSWER 1 OF 60  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:1028389  HCAPLUS
DOCUMENT NUMBER:         143:379156
TITLE:                   Selection and characterization of HIV-1 showing
                         reduced susceptibility to the non-peptidic protease
                         inhibitor tipranavir
AUTHOR(S):               Doyon, Louise; Tremblay, Sonia; Bourgon, Lise;
                         Wardrop, Elizabeth; Cordingley, Michael G.
CORPORATE SOURCE:        Research and Development, Biological Sciences
                         Department, Boehringer Ingelheim (Canada) Ltd., Laval,
                         QC, H7S 2G5, Can.
SOURCE:                  Antiviral Research (2005), 68(1), 27-35
                         CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Tipranavir is a novel, non-peptidic protease inhibitor, which possesses
     broad antiviral activity against multiple protease inhibitor-resistant
     HIV-1.  Resistance to this inhibitor however has not yet been well
     described.  HIV was passaged for 9 mo in culture in the presence of
     tipranavir to select HIV with a drug-resistant phenotype.
     Characterization of the selected variants revealed that the first
     mutations to be selected were L33F and I84V in the viral protease,
     mutations which together conferred less than two-fold resistance to
     tipranavir.  At the end of the selection expts., viruses harboring 10
     mutations in the protease (L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V,
     V82L, I84V) as well as a mutation in the CA/SP1 gag cleavage site were
     selected and showed 87-fold decreased susceptibility to tipranavir.  In
     vitro, tipranavir-resistant viruses had a reduced replicative capacity
     which could not be improved by the introduction of the CA/SP1 cleavage
     site mutation.  Tipranavir resistant viruses showed cross-resistance to
     other currently approved protease inhibitors with the exception of
     saquinavir.  These results demonstrate that the tipranavir resistance
     phenotype is associated with complex genotypic changes in the protease.
     Resistance necessitates the sequential accumulation of multiple mutations.
REFERENCE COUNT:         47    THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 60  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:666528  HCAPLUS
DOCUMENT NUMBER:         143:221830
TITLE:                   Novel 8-Substituted Dipyridodiazepinone Inhibitors
                         with a Broad-Spectrum of Activity against HIV-1
                         Strains Resistant to Non-nucleoside Reverse
```

Transcriptase Inhibitors

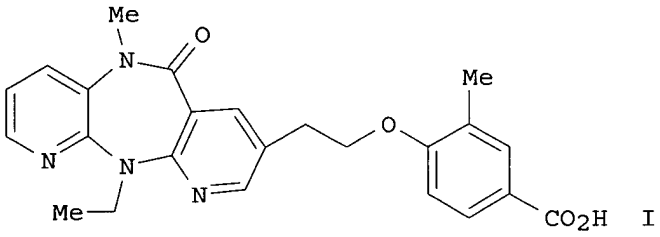
AUTHOR(S): O'Meara, Jeff A.; Yoakim, Christiane; Bonneau, Pierre R.; Boes, Michael; Cordingley, Michael G.; Deziel, Robert; Doyon, Louise; Duan, Jianmin; Garneau, Michel; Guse, Ingrid; Landry, Serge; Malenfant, Eric; Naud, Julie; Ogilvie, William W.; Thavonekham, Bounkham; Simoneau, Bruno

CORPORATE SOURCE: Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.

SOURCE: Journal of Medicinal Chemistry (2005), 48(17), 5580-5588
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



I

AB A series of novel 8-substituted dipyridodiazepinone-based inhibitors were investigated for their antiviral activity against wild type human immunodeficiency virus (HIV-1) and the clin. prevalent K103N/Y181C mutant virus. Our efforts have resulted in a series of benzoic acid analogs that are potent inhibitors of HIV-1 replication against a panel of HIV-1 strains resistant to nonnucleoside reverse transcriptase inhibitors (NNRTIs). Furthermore, the combination of good antiviral potency, a broad spectrum of activity, and an excellent pharmacokinetic profile provides strong justification for the further development of compound (I) as a potential treatment for wild type and NNRTI-resistant HIV-1 infection.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:191662 HCAPLUS

TITLE: Novel 8-substituted dipyridodiazepinone derivatives as HIV NNRTIs with broad antiviral potency

AUTHOR(S): Landry, Serge; Bonneau, Pierre R.; Bordeleau, Josee; Doyon, Louise; Duan, Jianmin; Guse, Ingrid; Malenfant, Eric; Naud, Julie; O'Meara, Jeff A.; Thavonekham, Bounkham; Yoakim, Christiane; Simoneau, Bruno; Bos, Michael; Cordingley, Michael G.

CORPORATE SOURCE: Boehringer Ingelheim (Canada) Ltd., Research & Development, Laval, QC, H7S 2G5, Can.

SOURCE: Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (2005), MEDI-329. American Chemical Society: Washington, D. C.
CODEN: 69GQMP

DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a potent component of highly active anti-retroviral therapies (HAART). More than 8 years after the introduction of nevirapine (the first NNRTI that was later joined by delavirdine and efavirenz), a new generation of NNRTI has yet to be approved for use in the clinic. In this drug class, the emergence of resistance is the major cause of treatment failure: Patients failing a first generation NNRTI are left without further NNRTI options because of cross-resistance to the entire class. There is therefore a therapeutic need for a next generation NNRTI that displays potent antiviral activity against wild-type and clin. observed NNRTI-resistant viruses associated with treatment failure. In addition, a convenient dosing regimen (once a day, low pill burden) must be achieved. The optimization of the C-8 substituent of dipyridodiazepinone derivs. led us to the identification of highly potent NNRTIs against wild-type virus, prevalent single and double mutants. The biol. activities, biopharmaceutical profile and the syntheses of these inhibitors will be discussed.

L6 ANSWER 4 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1008725 HCAPLUS
DOCUMENT NUMBER: 142:53401
TITLE: A novel model of HPV infection in meshed human foreskin grafts
AUTHOR(S): Duan, Jianmin; De Marte, Josie; Paris, William; Roopchand, Diana; Fleet, Tamara L.; Clarke, Jo-Anne; Yeong, Siu-Hong; Ferenczy, Alex; Katz, Murray; Cordingley, Michael G.
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Antiviral Research (2004), 64(3), 179-188
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study describes a novel meshing procedure that provided successful low-risk papillomavirus propagation and reproducible wart induction in human foreskin xenografts. The initial HPV6 and/or 11 inocula were collected from clin. excised human wart tissues and confirmed to be free of HPV16, 18 and 31 by PCR anal. Human foreskin grafts were collected from a circumcision clinic, and pre-inoculated with HPV virions by scarification. Meshing was carried out with a Zimmer Skin Grafter Mesher. Grafts were cut to appropriate size (1 cm + 1 cm or 5 mm + 5 mm) for cutaneous or s.c. grafting to NIH-nu-bg-xid mice under halothane anesthesia. Cutaneous xenografts were dressed with antibiotics and protective band-aids for 3 wk. In the paralleled experiment using the same viral stock containing both HPV6 and 11, and matched grafts, no visible papillomas were observed in non-meshed cutaneous xenografts (n = 4 up to 6 mo). In comparison, six of eight cutaneous xenografts treated with the meshing procedure formed visible papillomas within 4 mo. This high frequency of distinct papilloma induction over the surface of meshed xenografts were reproduced in subsequent expts. with viral stocks containing both HPV11 and 6 (8 out of 10 grafts), or with a single-type HPV11 inoculum (80-100%). In contrast, an initial viral stock of single-type HPV6 provided lower frequency and more delayed papilloma induction. Serial passage of HPV6 in the meshed xenograft appeared to improve both the induction frequency and growth rate up to the 3rd generation. Histol., in situ hybridization, and immunohistochem. anal. revealed similarity of xenograft warts to those observed in the clinic. The highly reproducible papilloma induction rate and successful viral stock

propagation associated with the meshing procedure provide a novel feature in the HPV xenograft model.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1008723 HCAPLUS
DOCUMENT NUMBER: 142:294546
TITLE: Isolation and characterization of herpes simplex virus type 1 resistant to aminothiazolylphenyl-based inhibitors of the viral helicase-primase
AUTHOR(S): Liuzzi, Michel; Kibler, Philip; Bousquet, Christiane; Harji, Fayaz; Bolger, Gordon; Garneau, Michel; Lapeyre, Nicole; McCollum, Robert S.; Faucher, Anne-Marie; Simoneau, Bruno; Cordingley, Michael G.
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, 2100, Can.
SOURCE: Antiviral Research (2004), 64(3), 161-170
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aminothiazolylphenyl-containing compds. BILS 179 BS and BILS 45 BS are novel inhibitors of the herpes simplex virus helicase-primase with antiviral activity in vitro and in animal models of HSV disease. To verify the mechanism of antiviral action, resistant viruses were selected by serial passage or by single-step plaque selection of HSV-1 KOS in the presence of inhibitors. Three resistant isolates K138r3, K22r5, and K22r1 were found to be 38-, 316-, and 2500-fold resistant to BILS 22 BS, a potent analog of BILS 45 BS. All 3 viruses had growth properties in vitro similar to wild-type HSV-1 KOS but they were sensitive to acyclovir. Cutaneous and intra-cerebral inoculation of mice with K22r1 or K22r5 resulted in pathogenicity equivalent to that of HSV-1 KOS. Both isolates were fully competent for reactivation from latency following corneal inoculation. Helicase-primase purified from cells infected with resistant viruses showed decreased inhibition in an in vitro DNA-dependent ATPase assay that correlated well with antiviral resistance. Marker transfer expts. and DNA sequence anal. identified single base pair mutations clustered in the N-terminus of the UL5 gene that resulted in single amino acid changes in the UL5 protein. Taken together, the results indicate that helicase-primase inhibitors prevent HSV growth by inhibiting HSV helicase-primase through specific interaction with the UL5 protein.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:657993 HCAPLUS
TITLE: Novel 8-substituted dipyridodiazepinone inhibitors with broad-spectrum of activity against NNRTI-resistant HIV-1
AUTHOR(S): Yoakim, Christiane; Bonneau, Pierre R.; Deziel, Robert; Doyon, Louise; Duan, Jianmin; Guse, Ingrid; Hache, Bruno; Landry, Serge; Malenfant, Eric; Naud, Julie; Ogilvie, William W.; O'Meara, Jeff A.; Plante, Raymond; Thavonekham, Bounkham; Simoneau, Bruno; Boes, Michael; Cordingley, Michael G.
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, Laval, QC, H7S 2G5, Can.
SOURCE: Abstracts of Papers, 228th ACS National Meeting,

Philadelphia, PA, United States, August 22-26, 2004 (2004), MEDI-129. American Chemical Society: Washington, D. C.
CODEN: 69FTZ8
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB HIV-1 reverse transcriptase is a key target for the inhibition of viral replication. However, treatment with regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTI), often lead to resistance due to drug-specific mutations, leaving patients with no further NNRTI options. Advanced 8-substituted dipyridodiazepinone derivs. were used as a starting point for the identification of new inhibitors with a broader antiviral profile and promising pharmacokinetic parameters. The cellular activity, biopharmaceutical and pharmacokinetic profiles of these novel analogs will be described.

L6 ANSWER 7 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:51812 HCAPLUS
DOCUMENT NUMBER: 140:287364
TITLE: Novel nevirapine-like inhibitors with improved activity against NNRTI-resistant HIV: 8-heteroarylthiomethyldipyridodiazepinone derivatives
AUTHOR(S): Yoakim, C.; Bonneau, P. R.; Deziel, R.; Doyon, L.; Duan, J.; Guse, I.; Landry, S.; Malenfant, E.; Naud, J.; Ogilvie, W. W.; O'Meara, J. A.; Plante, R.; Simoneau, B.; Thavonekham, B.; Bos, M.; Cordingley, M. G.
CORPORATE SOURCE: Department of Chemistry, Research & Development, Boehringer Ingelheim (Canada) Ltd, Lava, QC, 2100, Can.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(3), 739-742
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:287364
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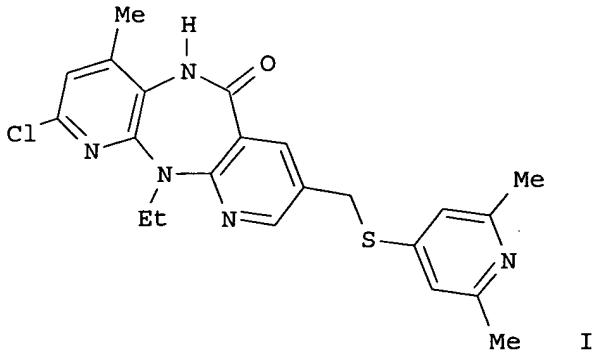


I

AB A series of 8-heteroarylthiomethyldipyridodiazepinone derivs. were prepared and evaluated for their antiviral profile against wild type virus and the

important K103N/Y181C mutant as an indicator for broad activity. 2,6-Dimethylpyridine derivative I was found to have a good pharmacokinetic profile in spite of poor metabolic stability in rat liver microsomes.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:907174 HCAPLUS
TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
AUTHOR(S): Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray; Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre; Boes, Michael; Cameron, Dale R.; Cartier, Mireille; Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau, Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace, Lisette; Laplante, Steven R.; Narjes, Hans; Poupart, Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St. George, Roger; Simoneau, Bruno; Steinmann, Gerhard; Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven M.; Yong, Chan-Loi; Llinas-Brunet, Montse
SOURCE: Nature (London, United Kingdom) (2003), 426(6964), 314
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
AB Unavailable
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:886572 HCAPLUS
DOCUMENT NUMBER: 140:122161
TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
AUTHOR(S): Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray; Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre; Boes, Michael; Cameron, Dale R.; Cartier, Mireille; Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau, Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace, Lisette; LaPlante, Steven R.; Narjes, Hans; Poupart, Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St. George, Roger; Simoneau, Bruno; Steinmann, Gerhard; Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven M.; Yong, Chan-Loi; Llinas-Brunet, Montse
CORPORATE SOURCE: Departments of Biological Sciences, Boehringer Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.
SOURCE: Nature (London, United Kingdom) (2003), 426(6963), 186-189
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is

essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of BILN 2061, a small mol. inhibitor biol. available through oral ingestion and the first of its class in human trials. Administration of BILN 2061 to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:634738 HCAPLUS
TITLE: Novel Nevirapine-like inhibitors with improved activity against NNRTI-resistant HIV: 8-heteroarylthiomethyldipyridodiazepinones derivatives
AUTHOR(S): O'Meara, Jeff A.; Bonneau, Pierre R.; Deziel, Robert; Doyon, Louise; Duan, Jianmin; Guse, Ingrid; Hache, Bruno; Landry, Serge; Malenfant, Eric; Naud, Julie; Ogilvie, William W.; Plante, Raymond; Simoneau, Bruno; Thavonekham, Bounkham; Yoakim, Christiane; Bos, Michael; Cordingley, Michael G.
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, Laval, QC, H7S 2G5, Can.
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-130. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Reverse transcriptase of HIV-1 is a key target for the inhibition of viral replication. However, upon treatment with a regiment containing non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistance often occurs due to drug-specific mutations. Advanced derivs. of the NNRTI nevirapine were used as a starting point for the identification of new inhibitors with broader antiviral profile. Synthesis, activity and biopharmaceutical profile of these 8-heteroarylthiomethyl analogs will be described.

L6 ANSWER 11 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:634736 HCAPLUS
TITLE: Identification of a novel series of Nevirapine-like NNRTIs with broad antiviral potency against mutant genotypes associated with treatment failure
AUTHOR(S): Landry, Serge; Bonneau, Pierre R.; Deziel, Robert; Doyon, Louise; Duan, Jianmin; Guse, Ingrid; Hache, Bruno; Malenfant, Eric; Naud, Julie; Ogilvie, William W.; O'Meara, Jeff A.; Plante, Raymond; Simoneau, Bruno; Thavonekham, Bounkham; Yoakim, Christiane; Bos, Michael; Cordingley, Michael G.
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, Laval, QC, H7S 2G5, Can.
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-128. American Chemical Society: Washington, D. C.
CODEN: 69EKY9

DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a potent component of highly active anti-retroviral therapies (HAART). With the currently approved NNTRIs, patients who fail treatment and develop resistance can not expect efficacy from any other NNRTIs, since all approved NNRTIs exhibit broad cross-resistance. There is therefore a therapeutic need for a second generation NNRTI having potent antiviral activity against HIV-1 wild-type and the most prevalent mutant genotypes associated with treatment failure. Using C-8 substituted analogs of Nevirapine as starting point, a series of potent inhibitors possessing a quinoline moiety were found to be highly potent against wild-type virus, as well as prevalent single and double mutants. The biol. activities, biopharmaceutical profile and the syntheses of these inhibitors will be discussed.

L6 ANSWER 12 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:634735 HCAPLUS
TITLE: Towards a second generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1 with broad spectrum of activity
AUTHOR(S): Thavonekham, Bounkham; Bonneau, Pierre R.; Cywin, Charles L.; Deziel, Robert; Doyon, Louise; Duan, Jianmin; Guse, Ingrid; Hache, Bruno; Hattox, Susan E.; Landry, Serge; Malenfant, Eric; Naud, Julie; Ogilvie, William W.; O'Meara, Jeff A.; Proudfoot, John R.; Plante, Raymond; Simoneau, Bruno; Yazdanian, Mehran; Yoakim, Christiane; Grob, Peter M.; Bos, Michael; Cordingley, Michael G.
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Research & Development, Laval, QC, H7S 2G5, Can.
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-127. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Treatment with nevirapine (like all NNRTIs) often results in the development of resistance due to mutation (s) in the RT enzyme. A pre-requisite for the next generation of NNRTI is potent antiviral activity against clin. prevalent NNRTI-resistant variants. Using C-8 substituted nevirapine analogs as a starting point, novel 8-heteroaryloxyethyl derivs. with broad antiviral activity have been identified. We will report herein the synthesis, the activity and the biopharmaceutical profile of these new derivs.

L6 ANSWER 13 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:625952 HCAPLUS
DOCUMENT NUMBER: 140:192243
TITLE: HPMPC therapy of MCMV-induced retinal disease in the SCID mouse measured by electroretinography, a non-invasive technique
AUTHOR(S): Garneau, Michel; Bolger, Gordon T.; Bousquet, Christiane; Kibler, Philip; Tremblay, Francois; Cordingley, Michael G.
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, 2100, Can.
SOURCE: Antiviral Research (2003), 59(3), 193-200
CODEN: ARSRDR; ISSN: 0166-3542

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of these studies was to investigate the use of non-invasive electroretinog. for the evaluation of retinal disease and its treatment in an ocular murine cytomegalovirus (MCMV) disease model. While under anesthesia, 102.6 plaque forming units (pfu) of salivary gland passaged, Smith strain MCMV was injected in the anterior chamber of 6- to 8-wk-old severe combined immunodeficiency (SCID) mice. At various times post-inoculation, bright-flash scotopic electroretinogram, viral titer, and histol. were obtained from the injected eye. Antiviral therapy was tested using 0.1 and 5 mg/kg/day s.c. injections of HPMPC (Cidofovir) once daily for 5 consecutive days. In infected animals, the a- and b-waves of the electroretinog. (ERG) signal were significantly reduced as of 10 days post-inoculation when compared to control animals. Therapy with HPMPC 0.1 mg/kg/day s.c. once daily for 5 consecutive days was able to delay the decrease in ERG wave amplitude and inhibit viral replication, whereas 5 mg/kg/day s.c. significantly protected the ERG, completely inhibited viral replication, and maintained ocular viral titer below the limit of detection for up to 17 days post-infection. The reduction of ERG activity during progression of retinal disease correlated well with reduction of disease pathol. ERG recording represents a valuable non-invasive technique to measure the progression of the retinal disease induced by MCMV and the efficacy of antiviral treatment in the ocular MCMV disease model.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:536943 HCAPLUS
DOCUMENT NUMBER: 139:239745
TITLE: Inhibition of Human Papillomavirus DNA Replication by Small Molecule Antagonists of the E1-E2 Protein Interaction
AUTHOR(S): White, Peter W.; Titolo, Steve; Brault, Karine; Thauvette, Louise; Pelletier, Alex; Welchner, Ewald; Bourgon, Lise; Doyon, Louise; Ogilvie, William W.; Yoakim, Christiane; Cordingley, Michael G.; Archambault, Jacques
CORPORATE SOURCE: Department of Biological Sciences, Boehringer Ingelheim Ltd., Laval, H7S 2G5, Can.
SOURCE: Journal of Biological Chemistry (2003), 278(29), 26765-26772
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human papillomavirus (HPV) DNA replication is initiated by recruitment of the E1 helicase by the E2 protein to the viral origin. Screening of our corporate compound collection with an assay measuring the cooperative binding of E1 and E2 to the origin identified a class of small mol. inhibitors of the protein interaction between E1 and E2. Isothermal titration calorimetry and changes in protein fluorescence showed that the inhibitors bind to the transactivation domain of E2, the region that interacts with E1. These compds. inhibit E2 of the low risk HPV types 6 and 11 but not those of high risk HPV types or of cottontail rabbit papillomavirus. Functional evidence that the transactivation domain is the target of inhibition was obtained by swapping this domain between a sensitive (HPV11) and a resistant (cottontail rabbit papillomavirus) E2

type and by identifying an amino acid substitution, E100A, that increases inhibition by .apprx.10-fold. This class of inhibitors was found to antagonize specifically the E1-E2 interaction in vivo and to inhibit HPV DNA replication in transiently transfected cells. These results highlight the potential of the E1-E2 interaction as a small mol. antiviral target.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:521336 HCAPLUS
DOCUMENT NUMBER: 139:239665
TITLE: Discovery of the first series of inhibitors of human papillomavirus type 11: inhibition of the assembly of the E1-E2-Origin DNA complex
AUTHOR(S): Yoakim, Christiane; Ogilvie, William W.; Goudreau, Nathalie; Naud, Julie; Hache, Bruno; O'Meara, Jeff A.; Cordingley, Michael G.; Archambault, Jacques; White, Peter W.
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(15), 2539-2541
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:239665
AB We have discovered a series of inhibitors of the assembly of the HPV11 E1-E2-origin DNA complex, which incorporate an indandione fused to a substituted THF.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:438555 HCAPLUS
DOCUMENT NUMBER: 139:223770
TITLE: Oral bioavailability and in vivo efficacy of the helicase-primase inhibitor BILS 45 BS against acyclovir-resistant herpes simplex virus type 1
AUTHOR(S): Duan, Jianmin; Liuzzi, Michel; Paris, William; Liard, Francine; Browne, Abigail; Dansereau, Nathalie; Simoneau, Bruno; Faucher, Anne-Marie; Cordingley, Michael G.
CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(6), 1798-1804
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study investigated the oral bioavailability and efficacy of BILS 45 BS, a selective herpes simplex virus (HSV) helicase-primase inhibitor, against acyclovir (ACV)-resistant (ACVr) infections mediated by the HSV type 1 (HSV-1) dlsptk and PAAr5 mutant strains. In vitro, the compound was more potent than ACV against wild-type clin. and laboratory HSV-1 strains and ACVr HSV isolates, as determined by a standard plaque reduction assay, with a mean 50% effective concentration of about 0.15 μM. The oral bioavailability of BILS 45 BS in hairless mice was 49%, with a peak concentration in plasma of 31.5 μM

after administration of a single dose of 25 mg/kg. Following cutaneous infection of nude mice, both the HSV-1 dlsptk and PAAr5 mutant strains induced significant, reproducible, and persistent cutaneous lesions that lasted for more than 2 wk. Oral treatment with ACV (100 or 125 mg/kg/day, three times a day by gavage) did not affect either mutant-induced infection. In contrast, BILS 45 BS at an oral dose of 100 mg/kg/day almost completely abolished cutaneous lesions mediated by both ACVr HSV-1 mutants. The 50% EDs of BILS 45 BS were 56.7 and 61 mg/kg/day against dlsptk- and PAAr5-induced infections, resp. Taken together, our results demonstrate very effective oral therapy of exptl. ACVr HSV-1 infections in nude mice and support the potential use of HSV helicase-primase inhibitors for the treatment of nucleoside-resistant HSV disease in humans.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:285586 HCAPLUS
DOCUMENT NUMBER: 137:179422
TITLE: Herpes simplex virus helicase-primase inhibitors are active in animal models of human disease
AUTHOR(S): Crute, James J.; Grygon, Christine A.; Hargrave, Karl D.; Simoneau, Bruno; Faucher, Anne-Marie; Bolger, Gordon; Kibler, Philip; Liuzzi, Michel; Cordingley, Michael G.
CORPORATE SOURCE: Research and Development Center, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA
SOURCE: Nature Medicine (New York, NY, United States) (2002), 8(4), 386-391
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Herpes simplex virus infections are the cause of significant morbidity, and currently used therapeutics are largely based on modified nucleoside analogs that inhibit viral DNA polymerase function. To target this disease in a new way, the authors have identified and optimized selective thiazolylphenyl-containing inhibitors of the herpes simplex virus (HSV) helicase-primase enzyme. The most potent compds. inhibited the helicase, the primase and the DNA-dependent ATPase activities of the enzyme with IC50 (50% inhibitory concentration) values less than 100 nM. Inhibition of the enzymic activities was through stabilization of the interaction between the helicase-primase and DNA substrates, preventing the progression through helicase or primase catalytic cycles. Helicase-primase inhibitors also prevented viral replication as demonstrated in viral growth assays. One compound, BILS 179 BS, displayed an EC50 (effective concentration inhibiting viral growth by 50%) of 27 nM against viral growth with a selectivity index greater than 2000. Antiviral activity was also demonstrated for multiple strains of HSV, including strains resistant to nucleoside-based therapies. Most importantly, BILS 179 BS was orally active against HSV infections in murine models of HSV-1 and HSV-2 disease and more effective than acyclovir when the treatment frequency per day was reduced or when initiation of treatment was delayed up to 65 h after infection. These studies validate the use of helicase-primase inhibitors for the treatment of acute herpesvirus infections and provide new lead compds. for optimization and design of superior anti-HSV agents.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:872224 HCAPLUS
DOCUMENT NUMBER: 136:183650
TITLE: Discovery, total synthesis, HRV 3C-protease inhibitory activity, and structure-activity relationships of 2-methoxystypandrone and its analogues
AUTHOR(S): Singh, Sheo B.; Graham, Pia L.; Reamer, Robert A.; Cordingley, Michael G.
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(24), 3143-3146
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:183650
AB 2-Methoxystypandrone, a naphthoquinone, was isolated from a Chinese herb Polygonum cuspidatum by bioassay guided fractionation using HRV 3C-protease assay. It showed an IC50 value of 4.6 μM and is moderately selective. A new 10-step, total synthesis of 2-methoxystypandrone was accomplished in 45% overall yield using a Diels-Alder approach. Several analogs of this compound were prepared Isolation, synthesis and HRV 3C-protease structure-activity relationships of these compds. have been described.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:482510 HCAPLUS
DOCUMENT NUMBER: 135:192119
TITLE: Characterization of recombinant HPV6 and 11 E1 helicases: effect of ATP on the interaction of E1 with E2 and mapping of a minimal helicase domain
AUTHOR(S): White, Peter W.; Pelletier, Alex; Brault, Karine; Titolo, Steve; Welchner, Ewald; Thauvette, Louise; Fazekas, Monika; Cordingley, Michael G.; Archambault, Jacques
CORPORATE SOURCE: Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Biological Chemistry (2001), 276(25), 22426-22438
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To better characterize the enzymic activities required for human papillomavirus (HPV) DNA replication, the E1 helicases of HPV types 6 and 11 were produced using a baculovirus expression system. The purified wild type proteins and a version of HPV11 E1 lacking the N-terminal 71 amino acids, which was better expressed, were found to be hexameric over a wide range of concns. and to have helicase and ATPase activities with relatively low values for Km(ATP) of 12 μM for HPV6 E1 and 6 μM for HPV11 E1. Interestingly, the value of Km(ATP) was increased 7-fold in the presence of the E2 transactivation domain. In turn, ATP was found to perturb the co-operative binding of E1 and E2 to DNA. Mutant and truncated versions of in vitro translated E1 were used to identify a minimal ATPase domain composed of the C-terminal 297 amino acids. This fragment was expressed, purified, and found to be fully active in ATP hydrolysis, single-stranded DNA binding, and unwinding assays, despite lacking the minimal origin-binding domain.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:28248 HCAPLUS
DOCUMENT NUMBER: 134:218570
TITLE: Purification and Biophysical Characterization of a Minimal Functional Domain and of an N-Terminal Zn2+-Binding Fragment from the Human Papillomavirus Type 16 E6 Protein
AUTHOR(S): Lipari, Francesco; McGibbon, Graham A.; Wardrop, Elizabeth; Cordingley, Michael G.
CORPORATE SOURCE: Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Biochemistry (2001), 40(5), 1196-1204
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The E6 Zn2+-binding protein of high-risk human papillomaviruses (HPVs) is one of the major transforming proteins encoded by these tumor viruses. A bacterial system was used to express wild type and truncated forms of HPV-16 E6 linked to GST. The recombinant proteins were released from GST through cleavage of a factor Xa site. Functional anal. of these proteins demonstrated that amino acids 2-142 comprise the minimal domain of E6 required to promote the degradation of p53 in vitro in a rabbit reticulocyte lysate. This purified protein, E6(Δ143-151), required a high salt concentration for maximum solubility, eluted as a monomer on gel filtration, and was shown to bind two Zn2+ ions by atomic absorption anal. An N-terminal subdomain of E6 (amino acids 2-77, E6-N) was similarly purified. Unlike E6(Δ143-151), E6-N was very soluble in low-salt buffers and hence was highly amenable to biophys. characterization. E6-N was shown to bind one Zn2+ ion by electrospray mass spectrometry and by atomic absorption anal. UV-visible spectroscopic anal. of Co2+-substituted E6-N revealed that four cysteine residues coordinate the metal ion. Mutational studies of all the cysteine residues in E6-N substantiated a critical role for Cys 30, 33, 63, and 66 in Zn2+ binding and in proper folding of the subdomain. Equilibrium sedimentation of E6-N demonstrated that it is a monomer, like E6(Δ143-151), at low concns., but dimerization occurs at high concns. (Kd = 0.1 mM). Finally, CD studies revealed significant secondary structure for both E6(Δ143-151) and E6-N. The results support a model of monomeric E6 possessing two functionally critical Zn2+-binding motifs.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:525806 HCAPLUS
DOCUMENT NUMBER: 133:234419
TITLE: Identification of domains of the human papillomavirus type 11 E1 helicase involved in oligomerization and binding to the viral origin
AUTHOR(S): Titolo, Steve; Pelletier, Alex; Pulichino, Anne-Marie; Brault, Karine; Wardrop, Elizabeth; White, Peter W.; Cordingley, Michael G.; Archambault, Jacques
CORPORATE SOURCE: Department of Biological Sciences, Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, H7S 2G5, Can.
SOURCE: Journal of Virology (2000), 74(16), 7349-7361

CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The E1 helicase of papillomavirus is required, in addition to host cell DNA replication factors, during the initiation and elongation phases of viral episome replication. During initiation, the viral E2 protein promotes the assembly of enzymically active multimeric E1 complexes at the viral origin of DNA replication. In this study we used the two-hybrid system and chemical crosslinking to demonstrate that human papillomavirus type 11 (HPV11) E1 can self-associate in yeast and form hexamers in vitro in a reaction stimulated by single-stranded DNA. Self-association in yeast was most readily detected using constructs spanning the E1 C-terminal domain (amino acids 353 to 649) and was dependent on a minimal E1-E1 interaction region located between amino acids 353 and 431. The E1 C-terminal domain was also able to oligomerize in vitro but, in contrast to wild-type E1, did so efficiently in the absence of single-stranded DNA. Sequences located between amino acids 191 and 353 were necessary for single-stranded DNA to modulate oligomerization of E1 and were also required, together with the rest of the C terminus, for binding of E1 to the origin. Two regions within the C-terminal domain were identified as important for oligomerization: the ATP-binding domain and region A, which is located within the minimal E1-E1 interaction domain and is one of four regions of E1 that is highly conserved with the large T antigens of simian virus 40 and polyomavirus. Amino acid substitutions of highly conserved residues within the ATP-binding domain and region A were identified that reduced the ability of E1 to oligomerize and bind to the origin in vitro and to support transient DNA replication in vivo. These results support the notion that oligomerization of E1 occurs primarily through the C-terminal domain of the protein and is allosterically regulated by DNA and ATP. The bipartite organization of the E1 C-terminal domain is reminiscent of that found in other hexameric proteins and suggests that these proteins may oligomerize by a similar mechanism.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 22 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:426600 HCAPLUS
DOCUMENT NUMBER: 133:346061
TITLE: Identification of Domains of the HPV11 E1 Protein Required for DNA Replication in Vitro
AUTHOR(S): Amin, Anthony A.; Titolo, Steve; Pelletier, Alex; Fink, Dominique; Cordingley, Michael G.; Archambault, Jacques
CORPORATE SOURCE: Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Virology (2000), 272(1), 137-150
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The HPV E1 and E2 proteins along with cellular factors, are required for replication of the viral genome. In this study the authors show that in vitro synthesized HPV11 E1 can support DNA replication in a cell-free system and is able to cooperate with E2 to recruit the host polymerase α primase to the HPV origin in vitro. Deletion anal. revealed that the N-terminal 166 amino acids of E1, which encompass a nuclear localization signal and a cyclin E-binding motif, are dispensable for E1-dependent DNA replication and for recruitment of pol α primase to the origin in vitro. A shorter E1 protein lacking the N-terminal 190

amino acids supported cell-free DNA replication at less than 25% the efficiency of wild-type E1 and was active in the pol α primase recruitment assay. An even shorter E1 protein lacking a functional DNA-binding domain due to a truncation of the N-terminal 352 amino acids was inactive in both assays despite the fact that it retains the ability to associate with E2 or pol α primase in the absence of ori DNA. The authors provide addnl. functional evidence that E1 interacts with pol α primase through the p70 subunit of the complex by showing that p70 can be recruited to the HPV origin by E1 and E2 in vitro, that the domain of E1 (amino acids 353-649) that binds to pol α primase in vitro is the same as that needed for interaction with p70 in the yeast two-hybrid system, and that exogenously added p70 competes with the interaction between E1 and pol α primase and inhibits E1-dependent cell-free DNA replication. On the basis of these results and the observation that pol α primase competes with the interaction between E1 and E2 in solution, the authors propose that these three proteins assemble at the origin in a stepwise process during which E1, following its interaction with E2, must bind to DNA prior to interacting with pol α primase. (c) 2000 Academic Press.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:400487 HCAPLUS

DOCUMENT NUMBER: 133:246858

TITLE: Topical effects of cidofovir on cutaneous rabbit warts: treatment regimen and inoculum dependence

AUTHOR(S): Duan, J.; Paris, W.; De Marte, J.; Roopchand, D.; Fleet, T.-L.; Cordingley, M. G.

CORPORATE SOURCE: Bio-Mega Research Division, Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.

SOURCE: Antiviral Research (2000), 46(2), 135-144
CODEN: ARSRDR; ISSN: 0166-3542

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present study examined topical effects of cidofovir on cutaneous rabbit warts. Based on an inoculum-dependency study, each New Zealand White rabbit was inoculated with a high and low titer of cottontail rabbit papillomavirus (CRPV) at four sites on each dorsolateral area. Inoculation with 50 ID50 induced papillomas at 100% of the inoculation sites within 16±1 days, and the wart growth curve plateaued within .apprx.7 wk. With an inoculum of 5 ID50, 80% of the inoculated sites developed papillomas within 21±1 days and their size plateaued at a later time. Cidofovir was applied topically twice daily on the inoculated sites at a concentration of 1% for 18 days, starting at three different time points. In the first experiment, treatment was initiated 7 days post-inoculation. One of the inoculated sides received cidofovir or the vehicle, PBS, while the other side was left untreated. With this treatment regimen, cidofovir significantly delayed the time of onset and the growth rate of papillomas induced with the high titer of inoculum. It completely prevented papilloma-induction on the sites inoculated with the low titer of CRPV. Reversible side-effects of cidofovir were observed on the directly treated area including erythema, necrosis, and flaking. Both therapeutic and side-effects were limited to the sites of direct exposure. In the second experiment, one of the two sides in each group of rabbits received cidofovir or vehicle starting on day 29 post-inoculation. With this treatment regimen, cidofovir significantly reduced wart growth against the low titer only. Topical treatment initiated on day 49

post-inoculation was not effective on warts initiated with either viral titer. These results demonstrated that topical cidofovir could be very effective against papillomavirus-induced wart growth if it is initiated early during the infection, especially against low titers of inoculum.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 24 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:8195 HCAPLUS
DOCUMENT NUMBER: 132:216586
TITLE: Acute murine cytomegalovirus infection: a model for determining antiviral activity against CMV induced hepatitis
AUTHOR(S): Bolger, G.; Lapeyre, N.; Rheaume, M.; Kibler, P.; Bousquet, C.; Garneau, M.; Cordingley, M.
CORPORATE SOURCE: Bio-Mega Research Division, Department of Biological Sciences, Boehringer Ingelheim (Canada) Limited, Laval, QC, Can.
SOURCE: Antiviral Research (1999), 44(3), 155-165
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute i.p. infection of weanling BALB/c mice with murine cytomegalovirus (MCMV) resulted in an inoculum titer-dependent weight loss, mortality and elevation of plasma transaminases (ALT: alanine transaminase and AST: aspartate transaminase). Three days post infection (p.i.) with 104.85 plaque forming units (pfu) there was 90% mortality with a mean death day p.i. of 4.1±0.2. Plasma levels of ALT and AST were elevated 24- and 15-fold, resp. Organ titers of virus (log10 pfu/g tissue) were 6.16 in the liver, 6.05 in the spleen, 4.0-4.7 in the lung, heart, kidney and intestine and undetectable in the muscle and brain. Organ concns. (units/g wet-weight) of ALT were highest in the liver, while for AST the highest levels were found in the heart. The concns. of ALT but not AST were reduced (35-55%) in the infected liver; the concns. of ALT and AST were not changed in other infected organs. There were excellent correlations (r0.95) between viral titers in the liver, increases of plasma ALT and depletion of liver ALT. HPMPC and ganciclovir administered either p.o. or s.c. reduced mortality, increases in plasma transaminases and viral burdens in the liver and prevented depletion of liver ALT. HPMPC was .apprx.10-fold more potent than ganciclovir. These results strongly suggest that i.p. infection of the BALB/c mouse with MCMV represents an animal model of CMV hepatitis that can be monitored by measuring plasma ALT.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:398688 HCAPLUS
DOCUMENT NUMBER: 131:180725
TITLE: Role of the ATP-binding domain of the human papillomavirus type 11 E1 helicase in E2-dependent binding to the origin
AUTHOR(S): Titolo, Steve; Pelletier, Alex; Sauve, Frederic; Brault, Karine; Wardrop, Elizabeth; White, Peter W.; Amin, Anthony; Cordingley, Michael G.; Archambault, Jacques
CORPORATE SOURCE: Department of Biological Sciences, Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd., Laval, H7S 2G5, Can.

SOURCE: Journal of Virology (1999), 73(7), 5282-5293
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Replication of the genome of human papillomaviruses (HPV) is initiated by the recruitment of the viral E1 helicase to the origin of DNA replication by the viral E2 protein, which binds specifically to the origin. We determined, for HPV type 11 (HPV-11), that the C-terminal 296 amino acids of E1 are sufficient for interaction with the transactivation domain of E2 in the yeast two-hybrid system and in vitro. This region of E1 encompasses the ATP-binding domain. Here we have examined the role of this ATP-binding domain, and of ATP, on E2-dependent binding of E1 to the origin. Several amino acid substitutions in the phosphate-binding loop (P loop), which is implicated in binding the triphosphate moiety of ATP, abolished E2 binding, indicating that the structural integrity of this domain is essential for the interaction. The structural constraints imposed on the E1 P loop may differ between HPV-11 and bovine papillomavirus type 1 (BPV-1), since the P479S substitution that inactivates BPV-1 E1 is tolerated in the HPV-11 enzyme. Other substitutions in the E1 P loop, or in two other conserved motifs of the ATP-binding domain, were tolerated, indicating that ATP binding is not essential for interaction with E2. Nevertheless, ATP-Mg stimulated the E2-dependent binding of E1 to the origin in vitro. This stimulation was maximal at the physiol. temperature (37°C) and did not require ATP hydrolysis. In contrast, ATP-Mg did not stimulate the E2-dependent binding to the origin of an E1 protein containing only the C-terminal domain (353 to 649) or that of mutant E1 proteins with alterations in the DNA-binding domain. These results are discussed in light of a model in which the E1 ATP-binding domain is required for formation of the E2-binding surface and can, upon the binding of ATP, facilitate and/or stabilize the interaction of E1 with the origin.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:173802 HCAPLUS
DOCUMENT NUMBER: 131:15618
TITLE: Inhibition of Human Cytomegalovirus Protease by Monocyclic β-Lactam Derivatives: Kinetic Characterization Using a Fluorescent Probe
AUTHOR(S): Bonneau, Pierre R.; Hasani, Firoz; Plouffe, Celine; Malenfant, Eric; LaPlante, Steve R.; Guse, Ingrid; Ogilvie, William W.; Plante, Raymond; Davidson, Walter C.; Hopkins, Jerry L.; Morelock, Maurice M.; Cordingley, Michael G.; Deziel, Robert
CORPORATE SOURCE: Departments of Biological Sciences and Chemistry Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of the American Chemical Society (1999), 121(13), 2965-2973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent reports have demonstrated the potential of monocyclic β-lactam derivs. as inhibitors of human cytomegalovirus (HCMV) protease. Investigation of the mechanism of inhibition by NMR and mass spectrometry has revealed the presence of an acylenzyme intermediate suggesting that β-lactams are hydrolyzed by the enzyme and cause inhibition by competing with substrate. The potential of a fluorogenic β-lactam

derivative for convenient kinetic characterization of this mechanism has been evaluated using 4S-(4-methylumbelliferone)-3R-methylazetidin-2-one-1-carboxylic acid (4-methylpyridyl) amide. Upon acylation of the enzyme, the fluorescent umbelliferone moiety is released, allowing for continuous monitoring of the hydrolytic process. Examination of a series of progress curves by numerical anal. has provided valuable information on acylation and deacylation rates which relate to the IC50 values observed for β-lactams. More importantly the potential of fluorescent probe as an active site titrating agent for HCMV protease has been exploited, and a simple protocol for rapid determination of active enzyme is described. The data
are consistent with the HCMV protease dimer being composed of two functional active sites. This titrating agent represents an important tool that should significantly facilitate the characterization of this novel enzyme.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 27 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:810928 HCAPLUS
DOCUMENT NUMBER: 130:149834
TITLE: Screening for herbicide resistance in black grass (Alopecurus myosuroides): a "ring" test
AUTHOR(S): Moss, S. R.; Albertini, A.; Arlt, K.; Blair, A.; Collings, L.; Bulcke, R.; Eelen, H.; Claude, J-P.; Cordingley, M.; Murfitt, R.; Gasquez, J.; Vacher, C.; Goodliffe, P.; Cranstone, K.; Kudsk, P.; Mathiassen, S.; De Prado, R.; Prosch, D.; Rubin, B.; Schmidt, O.; Walter, H.; Thuerwaechter, F.; Howard, S.; Turner, M.; Waelder, L.; Cornes, D.
CORPORATE SOURCE: IACR-Rothamsted, Herts, AL5 2JQ, UK
SOURCE: Mededelingen - Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen (Universiteit Gent) (1998), 63(3a), 671-691
CODEN: MFLBER; ISSN: 1373-7503
PUBLISHER: Universiteit Gent, Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to evaluate the consistency of resistance screening tests conducted by different organizations in order to improve the standardization of testing procedures. Ten samples of black grass (Alopecurus myosuroides) and a protocol were sent out to 16 different organizations and companies in eight countries. The test consisted of growing plants in pots, spraying at the 2-4 leaf stage with chlorotoluron (2.5 kg a.i./ha), isoproturon (1.0 kg a.i./ha), fenoxaprop-P-Et (68.75 g a.i./ha) and clodinafop-propargyl (60 g a.i./ha) and recording foliage fresh weight per pot, in addition to a visual assessment about 3-4 wk after spraying. There were 5 replicates and identical herbicide formulations and doses were used at all centers. The results for fenoxaprop and clodinafop were reasonably consistent between centers. All eight non-susceptible populations showed evidence of resistance to both herbicides. Four populations were identified as being consistently most resistant; two others least resistant. Results for chlorotoluron and isoproturon were more variable, although two populations were consistently resistant. Results for populations showing partial resistance were less consistent between centers, making interpretation more difficult. The two susceptible stds. were not equally sensitive to all the herbicides. Some of the atypical results could be explained by aspects of methodol., such as the use of sub-irrigation with soil acting herbicides. There was a

good correlation between visual assessments and those made on a foliage fresh weight basis. Recommendations for improving procedures for screening for resistance were made. A key recommendation was that standard susceptible and resistant reference populations should be included in every assay, and ideally every center should use identical stds. Regardless of how screening assays are conducted, the basis on which resistance is assigned should be stated.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:660824 HCAPLUS
DOCUMENT NUMBER: 130:104812
TITLE: Dose- and duration-dependence of ganciclovir treatment against murine cytomegalovirus infection in severe combined immunodeficient mice
AUTHOR(S): Duan, Jianmin; Paris, William; Kibler, Philip; Bousquet, Christiane; Liuzzi, Michel; Cordingley, Michael G.
CORPORATE SOURCE: Department of Biological Sciences, Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Antiviral Research (1998), 39(3), 189-197
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study investigates the full dose-response curve and treatment duration dependence of ganciclovir (GCV) against murine cytomegalovirus (MCMV) infection in severe combined immunodeficiency (SCID) mice. Animals inoculated i.p. with 6.3+103 pfu of MCMV per mouse developed typical wasting syndrome rapidly and died around day 12 post-inoculation. Once-daily treatment with s.c. GCV for 5 days dose dependently delayed MCMV-induced wasting syndrome and mortality at a dose range of 1-80 mg/kg per day, whereas a dose of 160 mg/kg per day induced reversible side-effects. The effect of GCV treatment on mean death day (MDD) was significantly correlated to redns. of viral titers in the lung ($r=0.969$, $P<0.05$). Treatment duration dependence was examined at the dose of GCV i.e. 80 mg/kg per day for 1, 5, 8 and 12 days. The protective duration, over vehicle-treated mice, was constantly 3-4 days plus the duration of GCV treatment, as evidenced by the delay of viral replication, wasting syndrome and death. At a sub-optimally ED of 10 mg/kg per day of GCV, maximum protection was achieved with an 8-day treatment regimen. Prolongation of this treatment to 12 days failed to further delay mean death day and wasting syndrome that started on day 10, indicative of insufficient suppression of viral replication. Treatment with a single dose of GCV failed to show a complete dose-response curve since only minimal protective effects were observed at the dose of 80 mg/kg while side-effects were associated with the dose of 160 mg/kg. The treatment duration dependence and requirement for sufficient dosage of GCV against CMV infection observed in the current model are consistent with clin. observations. It also suggests that 5-8 days treatment duration may be a good balance considering the opportunity for identifying active compds. and speeding up the turnaround time in drug evaluations.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 29 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:529697 HCAPLUS
TITLE: Helicase-primase inhibitors as novel anti-HSV agents.

AUTHOR(S): Simoneau, Bruno; Faucher, Anne-Marie; Bordeleau, Josee; Duceppe, Jean-Simon; Ghiro, Elise; Thavonekham, Bounkham; Xin, Zhili; Liuzzi, Michel; Bolger, Gordon; Duan, Jianmin; Cordingley, Michael G.
CORPORATE SOURCE: Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-212. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Herpes simplex viruses encode a helicase-primase enzyme that is essential for viral DN-A replication and virus growth. This enzyme unwinds duplex DNA and has DNA-dependent ATPase activity. It also synthesizes short oligo-ribonucleotide primers that are essential for the initiation of DNA synthesis by the viral polymerase. Using high throughput screening, substituted 4-phenylthiazole derivs. (1) have been identified as specific inhibitors of herpes simplex virus (HSV) type-1 helicase-primase. SAR studies have led to the identification of highly potent inhibitors that were also very effective in blocking viral replication in cell culture assays. Optimized inhibitors were also found to be orally active in animal models of HSV diseases. The SAR studies, biol. properties and syntheses of these inhibitors will be discussed.

L6 ANSWER 30 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:436287 HCAPLUS
DOCUMENT NUMBER: 129:183873
TITLE: Antiviral activity of a selective ribonucleotide reductase inhibitor against acyclovir-resistant herpes simplex virus type 1 in vivo
AUTHOR(S): Duan, Jianmin; Liuzzi, Michel; Paris, William; Lambert, Michelle; Lawetz, Carol; Moss, Neil; Jaramillo, Jorge; Gauthier, Jean; Deziel, Robert; Cordingley, Michael G.
CORPORATE SOURCE: Bio-Mega Research Division, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Antimicrobial Agents and Chemotherapy (1998), 42(7), 1629-1635
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study reports the activity of BILD 1633 SE against acyclovir (ACV)-resistant herpes simplex virus (HSV) infections in athymic nude (nu/nu) mice. BILD 1633 SE is a novel peptidomimetic inhibitor of HSV ribonucleotide reductase (RR). In vitro, it is more potent than ACV against several strains of wild-type as well as ACV-resistant HSV mutants. BILD 1633 SE. Its in vivo activity was tested against cutaneous viral infections in athymic nude mice infected with the ACV-resistant isolates HSV type 1 (HSV-1) dlsptk and PAAr5, which contain mutations in the viral thymidine kinase gene and the polymerase gene, resp. Following cutaneous infection of athymic nude mice, both HSV-1 dlsptk and PAAr5 induced significant, reproducible, and persistent cutaneous lesions that lasted for more than 2 wk. A 10-day treatment regimen with ACV given topically four times a day as a 5% cream or orally at ≤5 mg/mL in drinking water was partially effective against HSV-1 PAAr5 infection with a reduction of the area under the concentration-time curve (AUC) of 34 to 48%. The effects of ACV against HSV-1 dlsptk infection were not significant when it was administered topically and were only marginal when it was given in

drinking water. Treatment under identical conditions with 5% topical BILD 1633 SE significantly reduced the cutaneous lesions caused by both HSV-1 dlsptk and PAAr5 infections. The effect of BILD 1633 SE against HSV-1 PAAr5 infections was more prominent and was inoculum and dose dependent, with AUC redns. of 96 and 67% against infections with 106 and 107 PFU per inoculation site, resp. BILD 1633 SE also significantly decreased the lesions caused by HSV-1 dlsptk infection (28 to 51% AUC reduction). Combination therapy with topical BILD 1633 SE (5%) and ACV in drinking water (5 mg/mL) produced an antiviral effect against HSV-1 dlsptk and PAAr5 infections that was more than the sum of the effects of both drugs. This is the first report that a selective HSV RR subunit association inhibitor can be effective against ACV-resistant HSV infections in vivo.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:274542 HCAPLUS
DOCUMENT NUMBER: 129:37912
TITLE: Improved purification protocol of the HSV-1 protease catalytic domain, using immunoaffinity
AUTHOR(S): Mckercher, G.; Bonneau, P. R.; Lagace, L.; Thibeault, D.; Massariol, M. -J.; Krogsrud, R.; Lawetz, C.; Mcdonald, P. C.; Cordingley, M. G.
CORPORATE SOURCE: Bio-Mega Research Division, Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd., Laval, QC H7S 2G5, Can.
SOURCE: Biochemistry and Cell Biology (1997), 75(6), 795-801
CODEN: BCBIEQ; ISSN: 0829-8211
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The catalytic domain of herpes simplex virus protease was expressed in baculovirus-infected cells and purified in milligram quantities by ion-exchange and size-exclusion chromatog. The usefulness of this material was limited by the presence of a contaminating proteolytic activity, which caused time-dependent degradation of the protease. As a result, the authors decided to explore an alternative approach to purification Specific monoclonal antibodies were produced and evaluated by surface plasmon resonance as ligands for immunoaffinity chromatog. One monoclonal antibody, 6H4, was chosen for coupling to an affinity support, and the resulting column allowed the authors to obtain a pure and stable enzyme. Immunoaffinity chromatog. of herpes simplex virus type 1 protease resulted in successful elimination of the contaminating protease activity. Moreover, the immunoaffinity column permitted the isolation of stable and pure enzyme in a 1-column procedure.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 32 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:760319 HCAPLUS
DOCUMENT NUMBER: 128:112289
TITLE: Experiences from the structure determination of human cytomegalovirus protease
AUTHOR(S): Tong, Liang; Qian, Chungeng; Davidson, Walter; Massariol, Marie-Josee; Bonneau, Pierre R.; Cordingley, Michael G.; Lagace, Lisette
CORPORATE SOURCE: Boehringer Ingelheim Pharm., Inc., Ridgefield, CT, 06877, USA
SOURCE: Acta Crystallographica, Section D: Biological Crystallography (1997), D53(6), 682-690

CODEN: ABCRE6; ISSN: 0907-4449
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several obstacles were encountered and overcome during the structure determination of human cytomegalovirus protease. Dehydration of crystals, by exposing them to higher concns. of the precipitant, reduced the mosaicity of the crystals and may have also resolved their microscope twinning. The initial phase information was obtained with the seleno-methionyl multiple-wavelength anomalous diffraction (MAD) technique. However, site-specific mutagenesis was required to introduce extra Met residues into the protease. The phase information had to be improved by non-crystallog. symmetry averaging, initially among three crystal forms. A change in the composition of the artificial mother liquor led to a significant improvement, from 3.0 and 2.0 Å resolution, in the diffraction quality of the crystals. The experiences reported here may prove useful to structure determination of other proteins.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:386419 HCAPLUS
DOCUMENT NUMBER: 127:106503
TITLE: Self-association of herpes simplex virus type 1 ICP35 is via coiled-coil interactions and promotes stable interaction with the major capsid protein
AUTHOR(S): Pelletier, Alex; Do, Florence; Brisebois, Josee J.; Lagace, Lisette; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Biol. Sci., Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Journal of Virology (1997), 71(7), 5197-5208
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ordered copolymn. of viral proteins to form the herpes simplex virus (HSV) capsid occurs within the nucleus of the infected cell and is a complex process involving the products of ≥6 viral genes. In common with capsid assembly in double-stranded DNA bacteriophages, HSV capsid assembly proceeds via the assembly of an outer capsid shell around an interior scaffold. This capsid intermediate matures through loss of the scaffold and packaging of the viral genomic DNA. The interior of the HSV capsid intermediate contains the viral protease and assembly protein which compose the scaffold. Proteolytic processing of these proteins is essential for and accompanies capsid maturation. The assembly protein (ICP35) is the primary component of the scaffold, and previous studies have demonstrated it to be capable of intermol. association with itself and with the major capsid protein, VP5. Structural elements within ICP35 which are responsible for intermol. self-association and for interaction with VP5 were defined. Yeast (Saccharomyces cerevisiae) 2-hybrid assays and far-Western studies with purified recombinant ICP35 mapped a core self-association domain between Ser165 and His219. Site-directed mutations in this domain implicate a putative coiled coil in ICP35 self-association This coiled-coil motif is highly conserved within the assembly proteins of other alpha herpesviruses. In the 2-hybrid assay the core self-association domain was sufficient to mediate stable self-association only in the presence of addnl. structural elements in either N- or C-terminal flanking regions. These regions also contain conserved sequences which exhibit a high propensity for α helicity and may contribute to self-association by

forming addnl. short coiled coils. These data support a model in which ICP35 mols. have an extended conformation and associate in parallel orientation through homomeric coiled-coil interactions. In addnl. 2-hybrid expts. ICP35 mutants were evaluated for association with VP5. In addition to the C-terminal 25 amino acids of ICP35 previously shown to be required for VP5 binding, an addnl. upstream region was required. This region is between Ser165 and His234 and contains the core self-association domain. Site-directed mutations and construction of chimeric mols. in which the self-association domain of ICP35 was replaced by the GCN4 leucine zipper indicated that this region contributes to VP5 binding through mediating self-association of ICP35 and not through direct binding interactions. These results suggest that self-association of ICP35 strongly promotes stable association with VP5 in vivo and are consistent with capsid formation proceeding via formation of stable subassemblies of ICP35 and VP5 which subsequently assemble into capsid intermediates in the nucleus.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 34 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:579729 HCAPLUS
DOCUMENT NUMBER: 125:241643
TITLE: A new serine-protease fold revealed by the crystal structure of human cytomegalovirus protease
AUTHOR(S): Tong, Liang; Qian, Chungeng; Massariol, Marie-Josee; Bonneau, Pierre R.; Cordingley, Michael G.; Lagace, Lisette
CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, 06877, USA
SOURCE: Nature (London) (1996), 383(6597), 272-275
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human cytomegalovirus (HCMV), a herpesvirus, infects up to 70% of the general population in the United States and can cause morbidity and mortality in immunosuppressed individuals (organ-transplant recipients and AIDS patients) and congenitally infected newborns. HCMV protease is essential for the production of mature infections virions, as it performs proteolytic processing near the C-terminus (M-site) of the viral assembly protein precursor. HCMV protease is a serine protease, although it has little homol. to other clans of serine proteases. Here, the crystal structure of HCMV protease at 2.0 Å resolution is reported, and it is shown to possess a new polypeptide backbone fold. Ser-132 and His-63 are found in close proximity in the active site, confirming earlier biochem. and mutagenesis studies. The structure suggests that the third member of the triad is probably His-157. A dimer of the protease with an extensive interface is found in the crystal structure. This structure information will help in the design and optimization of inhibitors against herpesvirus proteases.

L6 ANSWER 35 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:46184 HCAPLUS
DOCUMENT NUMBER: 124:81893
TITLE: Resistance of herpes simplex virus type 1 to peptidomimetic ribonucleotide reductase inhibitors: selection and characterization of mutant isolates
AUTHOR(S): Bonneau, Anne-Marie; Kibler, Philip; White, Peter; Bousquet, Christiane; Dansereau, Nathalie; Cordingley, Michael G.
CORPORATE SOURCE: Bio-Mega/Boehringer Ingelheim Res. Inc., Laval, QC,

H7S 2G5, Can.
SOURCE: Journal of Virology (1996), 70(2), 787-93
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus (HSV) encodes its own ribonucleotide reductase (RR), which provides the high levels of deoxynucleoside triphosphates required for viral DNA replication in infected cells. HSV RR is composed of two distinct subunits, R1 and R2, whose association is required for enzymic activity. Peptidomimetic inhibitors that mimic the C-terminal amino acids of R2 inhibit HSV RR by preventing the association of R1 and R2. These compds. are candidate antiviral therapeutic agents. Here we describe the in vitro selection of HSV type 1 KOS variants with three- to nine-fold-decreased sensitivity to the RR inhibitor BILD 733. The resistant isolates have growth properties in vitro similar to those of wild-type KOS but are more sensitive to acyclovir, possibly as a consequence of functional impairment of their RRs. A single amino acid substitution in R1 (Ala-1091 to Ser) was associated with three-fold resistance to BILD 733, whereas an addnl. substitution (Pro-1090 to Leu) was required for higher levels of resistance. These mutations were reintroduced into HSV type 1 KOS and shown to be sufficient to confer the resistance phenotype. Studies in vitro with RRs isolated from cells infected with these mutant viruses demonstrated that these RRs bind BILD 733 more weakly than the wild-type enzyme and are also functionally impaired, exhibiting an elevated dissociation constant (Kd) for R1-R2 subunit association and/or reduced activity (Kcat). This work provides evidence that the C-terminal end of HSV R1 (residues 1090 and 1091) is involved in R2 binding interactions and demonstrates that resistance to subunit association inhibitors may be associated with compromised activity of the target enzyme.

L6 ANSWER 36 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:258642 HCAPLUS
DOCUMENT NUMBER: 122:111122
TITLE: Release analysis and its use in the optimization of the comminution and gravity circuits at the Wheal Jane tin concentrator
AUTHOR(S): Cordingley, M. G.; Hallewell, M. P.; Turner, J. W. G.
CORPORATE SOURCE: South Crofty plc, Redruth/Cornwall, TR15 3QN, UK
SOURCE: Minerals Engineering (1994), 7(12), 1517-26
CODEN: MENGEB; ISSN: 0892-6875
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Use of Release Anal. on data obtained from laboratory testwork carried out on a Mozley Laboratory Mineral Separator is a powerful technique for optimizing both gravity circuit performance and comminution requirements with respect to liberation size. This paper describes how the laboratory technique employed at Wheat Jane Mill has resulted in a significant improvement in the overall mill tin recovery.

L6 ANSWER 37 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:401334 HCAPLUS
DOCUMENT NUMBER: 121:1334
TITLE: Differential steroid hormone induction of transcription from the mouse mammary tumor virus promoter
AUTHOR(S): Archer, Trevor K.; Lee, Huay-Leng; Cordingley, Michael G.; Mymryk, Joe S.; Fragoso, Gilberto;

Berard, Diana S.; Hager, Gordon L.
CORPORATE SOURCE: Lab. Mol. Virology, Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Molecular Endocrinology (1994), 8(5), 568-76
CODEN: MOENEN; ISSN: 0888-8809
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mouse mammary tumor virus (MMTV) contains sequences in its proximal promoter region to which both glucocorticoid and progesterone receptors can bind. In transient transfection expts. both hormones are able to stimulate transcription from reporter plasmids containing either native or consensus hormone response elements (glucocorticoid response element/progesterone response element). Previous expts. have demonstrated that the MMTV long terminal repeat is reproducibly assembled into a phased array of nucleosomes when stably introduced into cells. Stimulation by glucocorticoids of endogenous templates led to a rapid but transient increase in transcription initiation and mRNA accumulation that can be correlated with increased sensitivity to restriction enzymes. In contrast, expts. using progesterone or a truncated glucocorticoid receptor failed to elicit a similar increase in mRNA levels as dexamethasone from stable chromatin templates. To understand this differential response, the authors have compared the responsiveness of MMTV promoter to glucocorticoids and progesterone when it is organized in either stable chromatin or in transiently acquired plasmids. The results demonstrate that the native chromatin structure prevents activation of this locus by progesterone, but permits stimulation by glucocorticoids.

L6 ANSWER 38 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:48867 HCAPLUS
DOCUMENT NUMBER: 120:48867
TITLE: Autoproteolysis of herpes simplex virus type 1 protease releases an active catalytic domain found in intermediate capsid particles
AUTHOR(S): Weinheimer, Steven P.; McCann, Patrick J., III; O'Boyle, Donald R., II; Stevens, John T.; Boyd, Branin A.; Drier, Diana A.; Yamanaka, Gregory A.; DiIanni, Carolyn L.; Deckman, Ingrid C.; Cordingley, Michael G.
CORPORATE SOURCE: Virol. Dep., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543-4000, USA
SOURCE: Journal of Virology (1993), 67(10), 5813-22
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The UL26 gene of herpes simplex virus type 1 (HSV-1) encodes a 635 amino acid protease that cleaves itself and the HSV-1 assembly protein ICP35cde (F. Liu and B. Roizman, J. Virol. 65:5149-5156, 1991). The authors previously examined the HSV protease by using an Escherichia coli expression system (I. C. Deckman, M. Hagen, and P. J. McCann III, J. Virol. 66:7362-7367, 1992) and identified two autoproteolytic cleavage sites between residues 247 and 248 and residues 610 and 611 of UL26 (C. L. DiIanni, D. A. Drier, I. C. Deckman, P. J. McCann III, F. Liu, B. Roizman, R. J. Colonno, and M. G. Cordingley, J. Biol. Chemical 268:2048-2051, 1993). In this study, a series of C-terminal truncations of the UL26 open reading frame was tested for cleavage activity in E. coli. The authors' results delimit the catalytic domain of the protease to the N-terminal 247 amino acids of UL26 corresponding to N0, the amino-terminal product of protease autoprocessing. Autoprocessing of the full-length protease was found to be unnecessary for catalysis, since elimination of either or both cleavage sites by site-directed mutagenesis fails to prevent cleavage of ICP35cd or

an unaltered protease autoprocessing site. Catalytic activity of the 247 amino acid protease domain was confirmed in vitro by using a glutathione-S-transferase fusion protein. The fusion protease was induced to high levels of expression, affinity purified, and used to cleave purified ICP35cd in vitro, indicating that no other proteins are required. By using a set of domain-specific antisera, all of the HSV-1 protease cleavage products predicted from studies in E. coli were identified in HSV-1-infected cells. At least two protease autoprocessing products, in addition to fully processed ICP35cd (ICP35ef), were associated with intermediate
B capsids in the nucleus of infected cells, suggesting a key role for proteolytic maturation of the protease and ICP35cde in HSV-1 capsid assembly.

L6 ANSWER 39 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:444997 HCAPLUS
DOCUMENT NUMBER: 119:44997
TITLE: The C-terminal third of UL42, a HSV-1 DNA replication protein, is dispensable for viral growth
AUTHOR(S): Sandra, Min Gao; Ditusa, F.; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543, USA
SOURCE: Virology (1993), 194(2), 647-53
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB UL42 is the herpes simplex virus type 1 DNA polymerase (Pol) accessory protein and is required for viral DNA replication and growth. Previous results demonstrated that the N-terminal two thirds of the protein contains all of the biochem. activities of the protein which can be measured in vitro. These activities includes dsDNA-binding, association with DNA polymerase, and stimulation of polymerase activity. To better understand the functions of UL42 in infected cells, two viral recombinants, UL42lacZ and n338, were isolated and characterized. In the mutant virus UL42lacZ, the UL42 gene was disrupted by insertion of the Escherichia coli lacZ gene, while in the mutant virus n338, a termination codon was introduced after amino acid position 338. Anal. of the mutant phenotypes suggest that (1) the first 338 residues of UL42 retain all the functions necessary for viral DNA replication and growth in lytic infection, (2) localization of UL42 to the cell nucleus is independent of Pol, and (3) localization of ICP8 (ssDNA-binding protein) to prereplication sites is independent of functional UL42.

L6 ANSWER 40 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:209336 HCAPLUS
DOCUMENT NUMBER: 118:209336
TITLE: Deletions of the carboxy terminus of herpes simplex virus type 1 UL42 define a conserved amino-terminal functional domain
AUTHOR(S): Tenney, Daniel J.; Hurlburt, Warren W.; Bifano, Marc; Stevens, John T.; Micheletti, Pamela A.; Hamatake, Robert K.; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543-4000, USA
SOURCE: Journal of Virology (1993), 67(4), 1959-66
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The herpes simplex virus type 1 UL42 protein was synthesized in

reticulocyte lysates and assayed for activity in vitro. Three functional assays were used to examine the properties of in vitro-synthesized UL42: (1) coimmunopptn. to detect stable complex formation with purified herpes simplex virus type 1 DNA polymerase (Pol), (2) a simple gel-based assay for DNA binding, and (3) a sensitive assay for the stimulation of Pol activity. UL42 synthesized in reticulocyte lysates formed a stable coimmunoprecipitable complex with Pol, bound to double-stranded DNA, and stimulated the activity of Pol in vitro. C-terminal truncations of the UL42 protein were synthesized from restriction enzyme-digested UL42 gene templates and gene templates made by PCR and assayed for in vitro activity. Truncations of the 488-amino-acid (aa) UL42 protein to aa 315 did not abolish its ability to bind to Pol and DNA or to stimulate Pol activity. Proteins terminating at aas 314 and 313 showed reduced levels of binding to Pol, but these and shorter proteins were unable to bind to DNA or to stimulate Pol activity. These results suggest that all three of the biochem. functions of UL42 colocalize entirely within the N-terminal 315 aas of the UL42 protein. Amino acid sequence alignment of alpha herpesvirus UL42 homologs revealed that the N-terminal functional doamin corresponds to the most highly conserved region of the protein, whereas the dispensable C terminus is not conserved. Conservative aa changes at the C terminus of the 315-aa truncated protein were used to show that conserved residues were important for activity. These results suggest that 173 aa of UL42 can be deleted without a loss of activity and that DNA-binding and Pol-binding activities are correlated with the ability of UL42 to stimulate Pol activity.

L6 ANSWER 41 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:142481 HCAPLUS
DOCUMENT NUMBER: 118:142481
TITLE: Identification of the herpes simplex virus-1 protease cleavage sites by direct sequence analysis of autoproteolytic cleavage products
AUTHOR(S): DiIanni, Carolyn L.; Drier, Diana A.; Deckman, Ingrid C.; McCann, Patrick J., III; Liu, Fenyong; Roizman, Bernard; Colonno, Richard J.; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543-4000, USA
SOURCE: Journal of Biological Chemistry (1993), 268(3), 2048-51
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus type-1 (HSV-1) encodes a protease responsible for proteolytic processing of the virus assembly protein, ICP35 (infected cell protein 35). The coding regions of ICP35 is contained within the gene that encodes the protease, and ICP35 shares amino acid identity with the carboxyl-terminal 329 amino acids of the protease. The HSV-1 protease was expressed in Escherichia coli as a fusion protein containing a unique epitope and the protein A Fc binding domain at its carboxyl terminus. The fusion protease underwent autoproteolytic cleavage at two distinct sites. The size of the cleavage products containing the carboxyl-terminal epitope mapped one cleavage site near the carboxyl terminus of the protease corresponding to the proteolytic processing site of ICP35, and the second site proximal to the amino terminus consistent with previous data. The carboxyl-terminal autoproteolytic cleavage products were partially purified on an IgG affinity column by virtue of the protein A Fc binding domain and subjected to direct amino-terminal sequence anal. Protein sequencing revealed that cleavage occurs between the Ala and Ser residues at amino acids 610/611 nad 247/248 of the HSV-1 protease. The flanking

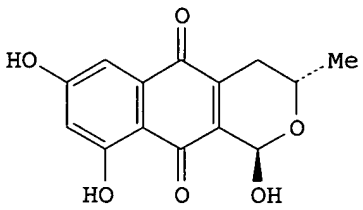
sequences share homol. with each other and are highly conserved in homologous proteases of other herpes viruses.

L6 ANSWER 42 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:56037 HCAPLUS
DOCUMENT NUMBER: 118:56037
TITLE: Mutations in the C terminus of herpes simplex virus type 1 DNA polymerase can affect binding and stimulation by its accessory protein UL42 without affecting basal polymerase activity
AUTHOR(S): Tenney, Daniel J.; Micheletti, Pamela A.; Stevens, John T.; Hamatake, Robert K.; Matthews, James T.; Sanchez, Anthony R.; Hurlburt, Warren W.; Bifano, Marc; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Virol., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543-4000, USA
SOURCE: Journal of Virology (1993), 67(1), 543-7
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of mutations in the herpes simplex virus type 1 DNA polymerase (Pol) C-terminal UL42 binding domain on the activity of Pol and its ability to form complexes with and be stimulated by UL42 were investigated in vitro. Wild-type Pol expressed in Saccharomyces cerevisiae was both bound and stimulated by UL42 in vitro. C-terminal truncations of 19 and 40 amino acids (aa) did not affect the ability of Pol to be stimulated by UL42 in vitro. This stimulation, as well as basal Pol activity in the presence of UL42, was inhibited by polyclonal anti-UL42 antiserum, thus indicating a phys. interaction between Pol and UL42. Removal of the C-terminal 59 aa of Pol and internal deletions of 72 aa within the Pol C terminus eliminated stimulation by UL42. None of the truncations or deletions within Pol affected basal polymerase activity. In contrast with their ability to be stimulated by UL42, only wild-type Pol and Pol lacking the C-terminal 19 aa bound UL42 in a coimmunopptn. assay. Thus, a functional UL42 binding domain of Pol is separable from sequences necessary for basal polymerase activity, and the C-terminal 40 aa of Pol appear to contain a region which modulates the stability of the Pol-UL42 interaction.

L6 ANSWER 43 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:422455 HCAPLUS
DOCUMENT NUMBER: 117:22455
TITLE: Structural implications of spectroscopic characterization of a putative zinc finger peptide from HIV-1 integrase
AUTHOR(S): Burke, Carl J.; Sanyal, Gautam; Bruner, Mark W.; Ryan, James A.; LaFemina, Robert L.; Robbins, Helen L.; Zeft, Andrew S.; Middaugh, C. Russell; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Pharm. Res., Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Biological Chemistry (1992), 267(14), 9639-44
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The N-terminal domain of human immunodeficiency virus (HIV-1) integrase (IN) contains the sequence motif His-Xaa3-His-Xaa23-Cys-Xaa2-Cys, which is strongly conserved in all retroviral and retrotransposon IN proteins. This structural motif constitutes a putative zinc finger in which a metal

ion may be coordinately bound by the His and Cys residues. A recombinant peptide, IN(1-55), composed of the N-terminal 55 amino acids of HIV-1 IN was expressed in Escherichia coli and purified. Utilizing a combination of techniques including UV-visible absorption, CD, Fourier transform IR, and fluorescence spectroscopies, it was shown that metal ions (Zn2+, Co2+, and Cd2+) are bound with equimolar stoichiometry by IN(1-55). The liganded peptide assumes a highly ordered structure with increased α-helical content and exhibits remarkable thermal stability. UV-visible difference spectra of the peptide-Co2+ complexes directly implicate thiols in metal coordination, and Co2+ d-d transitions in the visible range indicate that Co2+ is tetrahedrally coordinated. Mutant peptide containing conservative substitutions of one of the conserved His or either of the Cys residues displayed no significant Zn2+-induced conformational changes as monitored by CD and fluorescence spectra. It is concluded that the N terminus of HIV-1 IN contains a metal-binding domain whose structure is stabilized by tetrahedral coordination of metal by histidines 12 and 16 and cysteines 40 and 43. A preliminary structural model of this zinc finger is presented.

L6 ANSWER 44 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:41148 HCAPLUS
DOCUMENT NUMBER: 116:41148
TITLE: Structure and stereochemistry of thysanone: a novel human rhinovirus 3C-protease inhibitor from Thysanophora penicilloides
AUTHOR(S): Singh, Sheo B.; Cordingley, Michael G.; Ball, Richard G.; Smith, Jack L.; Dombrowski, Anne W.; Goetz, Michael A.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Tetrahedron Letters (1991), 32(39), 5279-82
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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AB The structure of thysanone (I), a novel naphthoquinone with a lactol ring was established on the basis of 1D and 2D NMR spectroscopy and confirmed by x-ray crystallog. anal. of its monomethyl ether. Thysanone showed an ED50 of 13 μg/mL against HRV 3C-protease.

L6 ANSWER 45 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:626895 HCAPLUS
DOCUMENT NUMBER: 115:226895
TITLE: Substrate specificity of recombinant human immunodeficiency virus integrase protein
AUTHOR(S): LaFemina, Robert L.; Callahan, Pia L.; Cordingley, Michael G.
CORPORATE SOURCE: Dep. Virus Cell Biol., Merck Sharp and Dohme Res.

Lab., West Point, PA, 19486, USA
SOURCE: Journal of Virology (1991), 65(10), 5624-30
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recombinant human immunodeficiency virus type 1 (HIV-1) integrase (IN) produced in Escherichia coli efficiently cleaves two nucleotides from the 3' end of synthetic oligonucleotide substrates which mimic the termini of HIV-1 proviral DNA. Efficient cleavage was restricted to HIV-1 substrates and did not occur with substrates derived from other retroviruses. Mutagenesis of the U5 long terminal repeat (LTR) terminus revealed only moderate effects of mutations outside the terminal four bases of the U5 LTR and highlighted the critical nature of the conserved CA dinucleotide motif shared by all retroviral termini. Integration of the endonuclease cleavage products occurs subsequent to cleavage, and evidence that the cleavage and integration reactions may be uncoupled is presented. Competition cleavage reactions demonstrated that IN-mediated processing of an LTR substrate could be inhibited by competition with LTR and non-LTR oligonucleotides.

L6 ANSWER 46 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:241550 HCAPLUS
DOCUMENT NUMBER: 114:241550
TITLE: Two regions of the mouse mammary tumor virus long terminal repeat regulate the activity of its promoter in mammary cell lines
AUTHOR(S): Lefebvre, Philippe; Berard, Diana S.; Cordingley, Michael G.; Hager, Gordon L.
CORPORATE SOURCE: Lab. Exp. Carcinog., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Molecular and Cellular Biology (1991), 11(5), 2529-37
CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In vivo expression of the mouse mammary tumor virus (MMTV) is restricted to a few organs, with the highest rate of transcription found in the mammary gland. Using a series of mammary and nonmammary murine cell lines, 2 regulatory elements were identified, located upstream of the hormone responsive element, that specifically regulate the MMTV promoter. The first element displays an enhancerlike activity and is coincident with the binding of a nuclear factor (designated MP4; position -1078 to -1052 in the long terminal repeat) whose presence is apparently restricted to mammary cell lines. The second regulatory region mediates a repressive activity and is mapped to the long terminal repeat segment from -415 to -483. This repression is specific for a particular subtype of mammary cells (RAC cells) able to grow under 2 differentiation states. The MMTV promoter in mammary cell lines thus appears to be modulated by 2 cis-acting elements that are likely to be involved in tissue-specific expression in vivo.

L6 ANSWER 47 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:115951 HCAPLUS
DOCUMENT NUMBER: 114:115951
TITLE: Transcription factor access is mediated by accurately positioned nucleosomes on the mouse mammary tumor virus promoter
AUTHOR(S): Archer, Trevor K.; Cordingley, Michael G.; Wolford, Ronald G.; Hager, Gordon L.
CORPORATE SOURCE: Lab. Exp. Carcinog., Natl. Cancer Inst., Bethesda, MD, 20892, USA

SOURCE: Molecular and Cellular Biology (1991), 11(2), 688-98
CODEN: MCEBD4; ISSN: 0270-7306
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A fragment of the mouse mammary tumor virus (MMTV) promoter was reconstituted from pure histones into a dinucleosome with uniquely positioned octamer cores. Core boundaries for the in vitro-assembled dinucleosome corresponded to the observed in vivo phasing pattern for long terminal repeat nucleosomes A and B. Nuclear factor 1 (NF1), a constituent of the MMTV transcription initiation complex, was excluded from the assembled dinucleosome, whereas the glucocorticoid receptor was able to bind. During transcription of MMTV in vivo, displacement of nucleosome B was necessary to permit assembly of the initiation complex. These results indicate that the nucleoprotein structure of the promoter can provide differential access to sequence-specific DNA-binding proteins and that active chromatin remodeling can occur during transcription activation.

L6 ANSWER 48 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:38099 HCAPLUS
DOCUMENT NUMBER: 114:38099
TITLE: Sequence-specific interaction of Tat protein and Tat peptides with the transactivation-responsive sequence element of human immunodeficiency virus type 1 in vitro
AUTHOR(S): Cordingley, Michael G.; LaFemina, Robert L.; Callahan, Pia L.; Condra, Jon H.; Sardana, Vinod V.; Graham, Donald J.; Nguyen, Tacy M.; LeGrow, Kathleen; Gotlib, Leah; et al.
CORPORATE SOURCE: Dep. Virus Cell Biol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1990), 87(22), 8985-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bacterially expressed Tat protein of human immunodeficiency virus type 1 binds selectively to short RNA transcripts containing the viral transactivation-responsive element (TAR). Sequences sufficient for Tat interaction map to the distal portion of the TAR stem-loop. Critical sequences for Tat binding are located in the single-stranded bulge, but no requirement for specific loop sequences could be demonstrated. TAR RNA competed for complex formation, and TAR mutants exhibited ≤10-fold reduced affinity for Tat. Synthetic peptides containing the basic region of Tat bound selectivity to TAR RNA and exhibited the same sequence requirements and similar relative affinities for mutant TAR RNA as the intact protein. These results suggest that Tat contains a small RNA-binding domain capable of recognizing TAR and implicate functional relevance for direct Tat-TAR interaction in transactivation.

L6 ANSWER 49 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:454904 HCAPLUS
DOCUMENT NUMBER: 113:54904
TITLE: Substrate requirements of human rhinovirus 3C protease for peptide cleavage in vitro
AUTHOR(S): Cordingley, Michael G.; Callahan, Pia L.; Sardana, Vinod V.; Garsky, Victor M.; Colonno, Richard J.
CORPORATE SOURCE: Dep. Virus Cell Biol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA

SOURCE: Journal of Biological Chemistry (1990), 265(16), 9062-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of synthetic peptides representing authentic proteolytic cleavage sites of human rhinovirus type 14 were assayed as substrates for purified 3C protease. Competition cleavage assays were employed to determine the relative specificity consts. (Kcat/Km) for substrates with sequences related to the viral 2C-3A cleavage site. Variable length peptides representing the 2C-3A cleavage site were cleaved with comparable efficiency. These studies defined a min. substrate of 6 amino acids (TLFQ/GP), although retention of the residue at position P5 (ETLFQ/GP) resulted in a better substrate by an order of magnitude. Amino acid substitutions at position P5, P4, P1', or P2' indicated that the identity of the residue at position P5 was not critical, whereas substitutions at position P4, P1' or P2' resulted in substrates with Kcat/Km values varying >2 orders of magnitude. In contrast to the 2C-3A cleavage site, small peptide derivs. representative of the 3A-3B cleavage site were relatively poor substrates, which suggested that residues flanking the min. core sequence may influence susceptibility to cleavage. The 3C protease of rhinovirus type 14 was also capable of cleaving peptides representing comparable cleavage sites predicted for coxsackie B virus and poliovirus.

L6 ANSWER 50 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:31626 HCAPLUS
DOCUMENT NUMBER: 112:31626
TITLE: Cleavage of small peptides in vitro by human rhinovirus 14 3C protease expressed in Escherichia coli
AUTHOR(S): Cordingley, Michael G.; Register, R. Bruce; Callahan, Pia L.; Garsky, Victor M.; Colonno, Richard J.
CORPORATE SOURCE: Dep. Virus Cell Biol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Virology (1989), 63(12), 5037-45
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 3C region of human rhinovirus 14 was expressed in E. coli. The microbially synthesized protease was functional, since the expressed precursor underwent autoproteolytic processing to generate mature mols. of the expected mol. weight and antigenicity. Mutation of the putative active-site Cys-146 residue to an alanine resulted in the synthesis of unprocessed precursor mols. Large quantities of the 20-kilodalton protease were purified by a simple purification protocol, and the resulting mol. was shown to be biol. active in vitro against synthetic peptides corresponding to the 2C-3A cleavage site. This site was cleaved with high efficiency and fidelity and was used to generate kinetic data on the 3C protease. The protease exhibited sensitivity to Zn2+, was capable of cleaving five of seven rhinovirus cleavage site peptides tested with variable efficiency, and could distinguish authentic substrate peptides from control peptides containing the dipeptide cleavage sequence pair Gln-Gly.

L6 ANSWER 51 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:171038 HCAPLUS
DOCUMENT NUMBER: 110:171038
TITLE: Neoplastic transformation and lineage switching of rat liver epithelial cells by retrovirus-associated oncogenes

AUTHOR(S): Garfield, Susan; Huber, Brian E.; Nagy, Peter; Cordingley, Michael G.; Thorgeirsson, Snorri S.
CORPORATE SOURCE: Lab. Exp. Carcinogen., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Molecular Carcinogenesis (1988), 1(3), 189-95
CODEN: MOCAE8; ISSN: 0899-1987
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumors produced by a chemical transformed rat liver epithelial (RLE) cell line and its single cell-derived clonal subpopulations demonstrate wide-ranging morphol. presentations including carcinomas, sarcomas, mixed epithelial-mesenchymal tumors, and undifferentiated tumors. To address the question of heterogeneity of tumors derived from transformed RLE cells, recombinant retroviruses were used containing the following transforming oncogenes: v-raf (3611-MSV), v-raf/v-myc (J2), v-myc (J5), and v-Ha-ras (pRNR16). All of the oncogenes, with the exception of v-myc (J5), were efficient transforming agents in the RLE cells. Tumors derived from the v-raf- and, to a lesser extent, those from v-Ha-ras-transformed RLE cells showed mixed epithelial-mesenchymal morphol., whereas the combination of v-raf/v-myc (J2) consistently produced differentiated trabecular carcinomas. Thus, the lineage commitment of the RLE cells can be perturbed by a single transforming oncogene and different tumor types derived from these cells may reflect the expression of a selective oncogene or a combination of oncogenes.

L6 ANSWER 52 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:2034 HCAPLUS
DOCUMENT NUMBER: 110:2034
TITLE: Expression and phenotypic alterations caused by an inducible transforming ras oncogene introduced into rat liver epithelial cells
AUTHOR(S): Huber, Brian E.; Cordingley, Michael G.
CORPORATE SOURCE: Wellcome Res. Lab., Research Triangle Park, NC, 27709, USA
SOURCE: Oncogene (1988), 3(3), 245-56
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although transforming ras oncogenes have been implicated as causative factors in liver cell transformation, the exact function and phenotypic alterations generated by the expression of such transforming genes in liver epithelial cells has yet to be defined. A retroviral vector system was used to deliver an inducible transforming ras gene into normal, anchorage-dependent rat liver epithelial cells. The Moloney murine sarcoma virus-based vector is composed of a dominant selectable marker, Neo, which is transcriptionally driven from the 5'-proviral long terminal repeat (LTR) and a transforming Ha-ras gene under the transcriptional control of a glucocorticoid-inducible LTR of the mouse mammary tumor virus. Subsequent to infection, G418 resistant, tumorigenic cell lines were isolated, and one particular cell line, designated REL-Ras3, was extensively characterized. Single copies of a full length as well as a truncated provirus were integrated into REL-Ras3 cells. The integrated ras gene was transcribed into poly(A+) RNA with dexamethasone treatment, increasing both the steady-state level of ras mRNA as well as transcription initiated from the MMTV LTR. Western blot anal. confirmed the presence of P21 containing a transforming mutation in position 12. Phenotypic alterations associated with ras expression in REL-Ras3 cells include: gross morphol. alterations; loss of contact inhibition of growth; becoming lethally tumorigenic and anchorage independent; alterations in

growth kinetics involving a diminished lag phase of the growth curve; and increases in glucose transport. Differences in growth kinetics and glucose transport could be directly correlated with the levels of ras expression.

L6 ANSWER 53 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:564466 HCAPLUS
DOCUMENT NUMBER: 109:164466
TITLE: A trans-acting factor negatively regulates transcription at the MMTV LTR
AUTHOR(S): Cordingley, Michael G.; Richard-Foy, H.; Lichtler, A.; Hager, Gordon L.
CORPORATE SOURCE: Lab. Exp. Carcinogenesis, NIH, Bethesda, MD, 20892, USA
SOURCE: UCLA Symposia on Molecular and Cellular Biology, New Series (1987), 52(Transcr. Control Mech.), 333-42
CODEN: USMBD6; ISSN: 0735-9543
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the absence of glucocorticoids, the promoter of mouse mammary tumor virus (MMTV) is markedly refractory to activation by a constitutive transcriptional enhancer. Oligonucleotide-directed mutations in the hormone-regulatory element (HRE) extensively impair the hormone response and allow effective activation of the promoter by the enhancer. This indicated that the HRE mediates neg. regulation of transcription in the absence of hormone. Expts. utilizing protein synthesis inhibitors revealed that a labile protein inhibits transcription initiation at the viral long terminal repeat region (LTR). Superinduction of transcription initiation results when protein synthesis is inhibited during hormone stimulation of the promoter. This effect is particularly dramatic when the enhancer of Harvey murine sarcoma virus is present at the upstream boundary of the MMTV LTR but is also observed in the absence of an enhancer element. Deletion of sequences which contain the HRE prevents superinduction. Apparently, a labile factor effects neg. regulation through sequences at or closely associated with the HRE and both pos. and neg. regulatory factors interact with closely associated sequences in the MMTV LTR.

L6 ANSWER 54 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:125435 HCAPLUS
DOCUMENT NUMBER: 108:125435
TITLE: Binding of multiple factors to the MMTV promoter in crude and fractionated nuclear extracts
AUTHOR(S): Cordingley, Michael G.; Hager, Gordon L.
CORPORATE SOURCE: Lab. Exp. Carcinog., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Nucleic Acids Research (1988), 16(2), 609-28
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hormone activation of mouse mammary tumor virus (MMTV) transcription results in the establishment of a tightly bound transcription factor complex at the promoter. Two fractionable binding activities which participate in this complex were characterized. One factor, previously identified as the mouse homolog of NF-1 (or CTF), protects sequences -82 to -56 from exonuclease III digestion in vitro. Sequences protected by a second factor (-42 to -4) span the TATA box of the promoter, suggesting that the binding activity in this fraction is equivalent to the HeLa cell transcription factor TFIID. The downstream boundary of exonuclease protection by the putative TATA-binding factor is -4; DNase 1 footprinting

of this fraction, however, showed addnl. protection of discrete sites downstream of the cap site. The apparent concentration and promoter-specific binding activity of both factors is unaffected by hormone treatment of the cells.

L6 ANSWER 55 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:50325 HCAPLUS
DOCUMENT NUMBER: 108:50325
TITLE: Molecular cloning and further characterization of cDNAs for rat nuclear-encoded cytochrome c oxidase subunits VIc and VIII
AUTHOR(S): Suske, Guntram; Mengel, Thomas; Cordingley, Mike; Kadenbach, Bernhard
CORPORATE SOURCE: Fachbereich Chem., Philipps-Univ., Marburg, D-3550, Fed. Rep. Ger.
SOURCE: European Journal of Biochemistry (1987), 168(1), 233-7
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A cDNA library was constructed from poly(A)-rich RNA of H35 rat hepatoma cells by insertion into λgt11. Screening with an antiserum to rat liver holocytochrome-c oxidase yielded 15 different recombinant clones. Eight clones were identified using monospecific antisera to individual subunits of the rat liver enzyme. The cDNA clones coding for subunits VIc and VIII were further characterized by DNA sequence anal. after subcloning in pUC8 and M13 mp9. The deduced amino acid sequences show 80% and 60% homol. to the corresponding bovine heart subunits, resp. Apparently, subunit VIc is not synthesized as a larger precursor mol. like most other mitochondrial proteins. The size of the mRNAs coding for subunits VIc and VII is .apprx.450 nucleotides, as revealed by Northern blot anal. with RNAs from different tissues. The clones were further used as probes for Southern blotting. Restricted high-mol.-mass DNA showed a complex pattern of bands indicating multigene families for both subunits in the rat genome.

L6 ANSWER 56 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:50206 HCAPLUS
DOCUMENT NUMBER: 108:50206
TITLE: Steroid-dependent interaction of transcription factors with the inducible promoter of mouse mammary tumor virus in vivo
AUTHOR(S): Cordingley, Michael G.; Riegel, Anna Tate; Hager, Gordon L.
CORPORATE SOURCE: Horm. Action Oncog. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cell (Cambridge, MA, United States) (1987), 48(2), 261-70
CODEN: CELLB5; ISSN: 0092-8674
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exonuclease protection in vivo was used as an assay to detect the interaction of nuclear factors with the steroid-inducible promoter of mouse mammary tumor virus. Binding of 2 factors is detected uniquely at the steroid-activated promoter, and results in protection of sequences between -82 and approx. +12. One factor is identified as the murine homolog of nuclear factor 1. The second (designated factor i) binds downstream of nuclear factor 1 and protects sequences extending over the cap site. Binding activities associated with both factors can be detected in crude nuclear exts.; their apparent concns. are unaffected by hormone treatment of the cells. These results demonstrate that glucocorticoid

induction of transcription results from receptor-mediated establishment of a transcription factor complex at the promoter rather than activation of a preexisting complex.

L6 ANSWER 57 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1984:449380 HCAPLUS
DOCUMENT NUMBER: 101:49380
TITLE: Analysis of DNA sequences which regulate the transcription of a herpes simplex virus immediate early gene
AUTHOR(S): Preston, Chris M.; Cordingley, Mike G.; Stow, Nigel D.
CORPORATE SOURCE: Virol. Unit, Med. Res. Counc., Glasgow, G11 5JR, UK
SOURCE: Journal of Virology (1984), 50(3), 708-16
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The locations and functions of DNA sequences involved in transcription of the gene encoding herpes simplex virus type 1 immediate early (IE) mRNAs 4 and 5 were analyzed by use of a transient-expression assay. The region upstream of the genes encoding IE mRNAs 4 and 5 was fused to the thymidine kinase gene coding sequences, and production of enzyme or RNA was measured after transfection of plasmids into BHK cells. The effect of deletions in the upstream region was determined in the absence or presence of a virus structural component which stimulates herpes simplex virus IE transcription. Two distinct units were identified. One of these was a promoter which required ≤69 base pairs of DNA specific for the genes encoding IE mRNAs 4 and 5 upstream from the mRNA 5' terminus. The other was a far-upstream region which mediated the response to the virion component and had an upstream boundary between nucleotides -347 and -335. An origin of DNA replication was interposed between these 2 units. The element TAATGAGATAC, which represents a consensus sequence present in the upstream regions of all herpes simplex virus type 1 IE genes, appeared to be essential for stimulation by the virion component. The activity of this element was modulated by the sequences which flank it, especially by regions having extremely high contents of guanine plus cytosine and which contain a conserved unit CCCGCCC or its complement GGGCGGG.

L6 ANSWER 58 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:433755 HCAPLUS
DOCUMENT NUMBER: 99:33755
TITLE: Functional analysis of a herpes simplex virus type 1 promoter: identification of far-upstream regulatory sequences
AUTHOR(S): Cordingley, Mike G.; Campbell, Moyra E. M.; Preston, Chris M.
CORPORATE SOURCE: Med. Res. Counc. Virol. Unit., Inst. Virol., Glasgow, G11 5JR, UK
SOURCE: Nucleic Acids Research (1983), 11(8), 2347-65
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A functional anal. was performed of DNA sequences upstream from the gene for immediate-early mRNA3 of herpes simplex virus type 1. Nucleotide sequences involved in initiation and pos. regulation of transcription were defined by construction of specific deletions in vitro. Transcription was assayed in vivo by microinjection into Xenopus oocytes or by introduction of plasmid DNA into tissue culture cells and measurement of transient expression. Three functional promoter elements were defined: (1) sequences between -16 and -37 which are not essential for transcription

but are required for accurate initiation; (2) proximal promoter sequences which are sufficient for transcription initiation in the absence of upstream sequences; and (3) far-upstream promoter sequences (>108 base pairs upstream) which increase transcription in oocytes and contain pos. regulatory sequences (-174 to -331) that respond strongly to a factor in the virus inoculum.

L6 ANSWER 59 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1982:539528 HCAPLUS
DOCUMENT NUMBER: 97:139528
TITLE: mRNA- and DNA-directed synthesis of herpes simplex virus-coded exonuclease in Xenopus laevis oocytes
AUTHOR(S): Preston, Chris M.; Cordingley, Mike G.
CORPORATE SOURCE: MRC Virol. Unit, Glasgow, G11 5JR, UK
SOURCE: Journal of Virology (1982), 43(2), 386-94
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Microinjection of herpes simplex virus (HSV)-infected cell mRNA into X. laevis oocytes resulted in the production of a new exonuclease [37228-74-3] activity. This enzyme strongly resembled the HSV alkaline exonuclease in many biochem. properties, and hybrid-arrested translation studies showed that it was virus coded, mapping at 0.080 and 0.185 genome map units. Exonuclease mRNA had a size and genome location equivalent to the mRNA encoding V185 in reticulocyte lysates, suggesting that V185 is the exonuclease. The enzyme synthesized in oocytes acted as an exonuclease in vivo. Two plasmids containing HSV DNA fragments directed the synthesis of exonuclease when microinjected into oocyte nuclei, and this finding enabled the coding and control sequences for this gene to be localized to 0.155 to 0.185 genome map units.

L6 ANSWER 60 OF 60 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1981:546915 HCAPLUS
DOCUMENT NUMBER: 95:146915
TITLE: Transcription and translation of the herpes simplex virus type 1 thymidine kinase gene after microinjection into Xenopus laevis oocytes
AUTHOR(S): Cordingley, Mike G.; Preston, Chris M.
CORPORATE SOURCE: MRC Virol. Unit, Glasgow, G11 5JR, UK
SOURCE: Journal of General Virology (1981), 54(2), 409-14
CODEN: JGVIAY; ISSN: 0022-1317
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hybrid plasmid pTK1 consists of the herpes simplex virus type 1 (HSV-1) BamHI p fragment, which contains the thymidine kinase (TK) gene, inserted into the vector pAT153. When pTK1 DNA was microinjected into nuclei of X. laevis oocytes, functional HSV-1-specific TK was produced, showing that transcription and translation of the gene occurred. Investigation of pTK1-specific RNA by Southern blot hybridization revealed that all regions of the hybrid plasmid were transcribed by RNA polymerase II, but sequences present in TK mRNA were most highly represented in stable transcripts.

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